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Peter L. Munk
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Interventional Radiology in Palliative Care

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Peter L. Munk • Suresh B Babu
Editors

Interventional Radiology in Palliative Care

Springer

Editors
Peter L. Munk
Vancouver General Hospital
Vancouver Coastal Health Research Institute
Vancouver, BC, Canada

Suresh B Babu
Department of Diagnostic Radiology
Khoo Teck Puat Hospital
Yishun Central
Singapore, Singapore

ISSN 0942-5373 ISSN 2197-4187 (electronic)
Medical Radiology
ISBN 978-3-030-65462-7 ISBN 978-3-030-65463-4 (eBook)
https://doi.org/10.1007/978-3-030-65463-4

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This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

It gives me great personal pleasure to write the Foreword for this book, *Interventional Radiology in Palliative Care*. The idea for proposing this book was not difficult. Professor Peter L. Munk, my good friend of more than 20 years standing and senior author of this book, has, over the recent few years, gained prominence speaking on musculoskeletal (MSK) interventional radiology (IR) procedures in palliative care at conferences in different parts of the world. With the field of palliative care growing in importance, and the expanding and increasingly vital role of IR in treating these patients, it is logical to see the need for a book that comprehensively addresses this niche area.

The lead author Dr Suresh B Babu is a respected senior interventional radiologist in Singapore and serves as IR Chief at Khoo Teck Puat Hospital (KTPH), Singapore. As geriatric medicine is one of the leading clinical subspecialties in KTPH, the IR team has extensive experience dealing with patients needing palliative treatment. Suresh knows Peter well, having done his IR Fellowship at Vancouver General Hospital (VGH), University of British Columbia (UBC), many years ago, when he was still practicing in the UK.

Over the past two decades, many young Singaporean radiologists from various local hospitals did their advanced Fellowships in VGH/UBC, particularly in MSK radiology and IR; and many Canadian radiologists have visited Singapore as faculty and visiting experts. This book mirrors our close Singapore-Canadian links, supplemented by contributions from experts hailing from top centers in the UK, France, and the USA.

The organization of *Interventional Radiology in Palliative Care* reflects the vast experience of the two senior authors and the importance of collaboration with clinical colleagues, particularly palliative care physicians. Following introductions of palliative care and IR in general, key topics—clinical outcome measures, ethics, consent and communication, and nutrition—are addressed. The book then turns to focused approaches to problem-solving, providing solutions to many specific topics relating to musculoskeletal and neurological pain relief, tumor debulking, bleeding, and obstruction in various hollow organs. Drainages in different parts of the body are dealt with in detail, as are fistula treatment and finally, intrathecal pain pumps.

This book will be valuable not only to interventional radiologists, palliative care physicians, and oncologists, but will be useful to all other

professionals caring for and aiming to provide their patients with an improved quality of life, albeit under inherently difficult circumstances. With a globally ageing population on the rise, the need for palliative care treatment options will be expected to increase.

October 2020 Singapore

Wilfred C. G. Peh
Department of Diagnostic Radiology
Khoo Teck Puat Hospital
Singapore, Singapore

Yong Loo Lin School of Medicine
National University of Singapore
Singapore, Singapore

Preface

Over the last generation, huge advances in Interventional Radiology (IR) have occurred, revolutionizing the way we treat innumerable medical conditions. Not a year goes by without new procedures being devised to address ever more clinical situations. Even for those of us in Radiology, it is often hard to keep up with these improvements.

A number of months ago, we were approached by our colleague and friend Professor Wilfred Peh of the National University of Singapore and Khoo Teck Puat Hospital, Singapore, who in his capacity as Book Series Editor for Springer, first proposed the idea for this book. He pointed out that relatively little existed on the market that addressed the needs that existed in the field of Palliative Care that could be addressed using the skills and experience that has been accrued by IR.

Bouncing the idea off our Palliative Medicine colleagues, two things became apparent. First, clinicians who referred their patients for imaging-guided IR procedures are generally appreciative of the positive impact these procedures have on their patient's quality of life. IR procedures make end-of-life care much more successful and easier. Second, it was clear that many Palliative Medicine physicians (and other clinicians involved in care of patients receiving palliative care) are often poorly informed about what IR can do to facilitate end-of-life care of their patients.

This book represents the consequence of these many discussions. What follows is the combined experience and wisdom of many IR radiologists and Palliative Medicine physicians from around the world. Without the shared experience and knowledge of these contributors, this book would have never seen the daylight.

First and foremost, we hope that this book may facilitate the delivery of care that will improve the quality of life for our patients. We also hope that it will inspire those performing procedures to expand their repertoire thereby further expanding what they are able to do for their patients. Finally, we hope this will give Palliative Care physicians a broader idea of the many clinical situations where IR can augment the care of their patients.

Our project coordinators, Ms Shanti Ramamoorthy and Mr M. Vignesh are the guiding lights for this book. They constantly dragged us to the right path and set us on it. We also wish to acknowledge support and guidance from the Springer Management Team, Ms Barbara Zoehrer and Ms Rosemarie Unger. We also wish to acknowledge the support and succour provided by our family. I (Peter L. Munk) have always depended on and greatly treasured the

encouragement of my wife Maria Chung and our three daughters Charlotte, Eleanor, and Sophie Munk. I (Suresh B Babu) am grateful for the life support given to me by Saraswathy, Sophie, Sammie, Sashti, and Sharvi Babu.

This would not have been possible without the strong support from our friends and colleagues, from our respective departments, from Vancouver and Singapore, and you know who you are. Thank You!

We are grateful to our patients, teachers, and colleagues for teaching us medicine, guiding us through our careers, and letting us practice this healing art of advanced speciality IR. To the patients!

Vancouver, BC, Canada — Peter L. Munk
Singapore, Singapore — Suresh B Babu

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Part I

Introduction and Nutrition

Introduction to Palliative Care

Pippa Hawley

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Abstract

Interventional radiological techniques are proving to be vital in the relief of physical suffering and improving function, both of which are also goals for modern palliative care. The need for all medical specialties to be able to deliver at least basic palliative care as a core competency is now widely recognized. A Palliative Approach to Care provided by a diverse range of health care professionals from the time of diagnosis can meet the needs of most patients and their families living with serious illnesses, allowing Specialist Palliative Care services to take care of those with the most complex needs. Palliative care primarily impacts three domains: symptom management, communication around goals of care,

P. Hawley (✉)
UBC Division of Palliative Care,
UBC Department of Medicine,
Pain and Symptom Management/Palliative Care Program, BC Cancer, Vancouver,
BC, Canada
e-mail: phawley@bccancer.bc.ca

© Springer Nature Switzerland AG 2021

P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_1

and collaboration between all the different people and services involved. Awareness of how interventional radiologists, anesthesiologists and specialist palliative care teams can collaborate is particularly important when carrying out procedures on people with complex needs who are suffering greatly. A common understanding of the principles of palliative care will facilitate future integration throughout the health care system so that the relief of suffering for our most vulnerable patients is promptly achieved, whatever their prognosis.

1 Introduction

Suffering is experienced by persons, not merely by bodies, and has its source in challenges that threaten the intactness of the person as a complex social and psychological entity. Suffering can include physical pain but is by no means limited to it. The relief of suffering and the cure of disease must be seen as twin obligations of a medical profession that is truly dedicated to the care of the sick. Physicians' failure to understand the nature of suffering can result in medical intervention that (though technically adequate) not only fails to relieve suffering but becomes a source of suffering itself (Cassel 1982).

Being diagnosed with a life-threatening disease causes suffering in physical, psychological, social and spiritual domains, but one could presume that the most extreme suffering we see would be seen in those who choose Medical Assistance in Dying (MAiD).

In Canada, where MAiD has been legal since 2016, the majority of recipients have been cancer patients and the most common reasons for choosing this mode of death are:

- Loss of control and independence
- Loss of ability to do enjoyable and meaningful activities
- Fear of future suffering
- Illness-related physical suffering

For every patient who actually goes through with MAiD there are many who consider it, and for most of them it is the fear of future suffering that is the primary source of distress.

2 What Is Palliative Care?

Palliative Care can be described briefly as a way of caring for people with life-threatening illnesses which focuses on quality of life. The definitions used by the World Health Organization (https://www.who.int/cancer/palliative/definition/en/), Canadian Society of Palliative Care Physicians (http://www.cspcp.ca/wp-content/uploads/2016/11/Full-Report-How-to-Improve-Palliative-Care-in-Canada-FINAL-Nov-2016.pdf), and the US's Centre to Advance Palliative Care (https://www.capc.org/about/palliative-care/websites) all describe palliative care similarly, as an approach to care that addresses patient needs in the physical, social, psychological, and spiritual domains. Three main components are described:

1. Meticulous prevention and management of symptoms, including pain
2. Excellence in communication, in discussion of goals of care and advance care planning
3. An extra layer of support for practical needs, particularly with respect to care provided at the patient's home

3 Why Is This Important for Interventional Radiologists?

Patients receiving curative and palliative disease-modify treatments are generally ambulatory, and the most cost-effective way of meeting their needs will be in the outpatient clinic setting.

Minimally invasive palliative procedures have a very important role in the prevention and management of pain and loss of function, especially in cancer, and can keep patients in a state of comfort and functional capacity to allow them to stay

at home. A coordinated Palliative Care strategy to minimize suffering for people with serious illnesses should include patients having timely access to a wide range of palliative procedures. Interventional radiologists are very much a part of a modern integrated interprofessional/multidisciplinary palliative care team. In order to become part of the team, radiologists must have at least basic palliative care skills, and have an understanding of the nature of modern palliative care when communicating with patients and colleagues of all disciplines.

4 The History of Palliative Care

The first known "hospice" was opened as a refuge for travelers and the sick by the Order of the Knights Hospitaller of St. John of Jerusalem in Rhodes. The concept was adopted by the Catholic Church and the hospice of L'Association des Dames de Calvaire was founded by Jeanne Garnier in1843, focusing on lepers, the destitute, and the dying. Other hospices were opened by other church-associated charities, particularly in the USA, Australia, Ireland, and England in the 1800s, extending their reach to include people suffering from tuberculosis and incurable cancer.

Based on knowledge of the effects of opium, morphine was invented in the 1820s, initially only as an injectable liquid, and the combination of poor hypodermic syringe and needle technology with widespread recognition of opioids in the addiction context did not make it an attractive proposition as an analgesic. The first modern hospice (St. Christopher's) was founded by Dame Cicely Saunders in London, England in 1967, after Dr. Saunders realized that people who were dying needed a different approach to care than was the norm in health care at the time, which focused very much on disease management.

The appearance of orally administered morphine was a key facilitator in this. Physicians from all over the world visited St Christopher's and brought back De. Saunders' ideas, leading to the opening of similar centers around the world, some of the earliest being in Canada. The term "Palliative Care" (in French: Soin Palliatif) was actually coined by Canadian urologist Dr. Balfour Mount in the 1970s because of the historical associations of the term "Hospice" in the Canadian francophone community. This renaming facilitated the spread of palliative care programs around the world in the latter part of the twentieth century, and originally the term served its purpose well. Palliative Care Units opened in many hospitals. Though small in number of beds, their impact was leveraged by outreach from staff in these units to provide consultation, education, and research throughout the health care environment, and the opening of residential hospices was made possible by volunteers and philanthropists.

5 The "Upstreaming" of Palliative Care

The start of the twenty-first century coincided with a growing awareness of the benefits of having access to palliative care early in the course of illness, with some seminal clinical trials demonstrating not just the expected improvements in symptom severity and quality of life of patients and their caregivers/loved ones, but also a reduction in use of inappropriate interventions in the last weeks of life (like ICU admissions and chemotherapy), but also reductions in the costs of care without any shortening of survival. In fact, early palliative care intervention studies usually showed longer survival for recipients. This attracted the attention of health care administrators keen to reduce health care spending without perception of loss of care quality. Unfortunately, many patients accessed these programs very late in their illness, and for many it was too late to achieve the maximum potential benefits from this kind of care. One of the most challenging barriers to early access to palliative care was the understandable general perception that palliative care and hospice programs were only appropriate for people who were dying. Originally synonymous, and in the absence of any new language, a need

for separation of the terms Palliative Care and Hospice began to emerge.

Contrary to what many people believe, modern palliative care can be provided *alongside* treatments targeting the underlying disease and may be needed from the time of diagnosis. Similarly, treatments targeting control of disease may be required alongside palliative care, right up to the time of death. Both approaches are necessary and should have equal value, whether in a high resource health care system with many treatment options, or in a developing setting where patients are diagnosed late in the course of illness and few curative treatments are available.

Advances in medicine, for example in antiviral drugs, organ transplantation, and oncology treatments, have changed the landscape for many people with what used to be thought of as inevitably fatal diseases. Hopefully similar advances in other illnesses such as neurodegenerative and hereditary disease will be following through the lifetimes of you, the readers, but these amazing advances come inextricably packaged with increasing confusion about what to expect as we age. Acceptance of our mortality is becoming progressively more hampered by uncertainty. A sense of needing to "never give up" is pervasive in the media, with patients and their loved ones vacillating between needing to prepare for death whilst simultaneously having a potentially realistic hope for survivorship on a daily basis.

Modern palliative care includes hospice care, including end of life care, but also includes early integrated supportive care from the time of diagnosis, and as modern medical treatments progress, it is clear that at least some patients will actually survive their illness, transitioning to survivorship through a period of rehabilitation, when the prognosis can be very uncertain.

This concept of need for simultaneous disease-targeting and palliative approaches to care has taken a long time to become established, especially in areas other than cancer care. Though the AIDS epidemic in the 1980s and 90s did lead to the opening of some hospices and palliative care programs that did not focus on cancer patients, the needs of people with other life-threatening chronic conditions such as heart or kidney failure, chronic lung disease and neurodegenerative diseases are only relatively recently starting to acknowledge the need for a palliative approach to care and to access support from specialist palliative care programs.

This new model of care for patients with serious illnesses is illustrated in the "Bow Tie Model of Twenty-First Century Palliative Care" (Hawley 2014) (Fig. 1).

The words used in the model can be adjusted to different cultures, but the basic principle the model tries to convey is the need acknowledge the possibility of survivorship in order to engage patients early enough in the course of their illness to make a difference to outcomes. This can be communicated to patients and families as "hope for the best, and prepare for the rest."

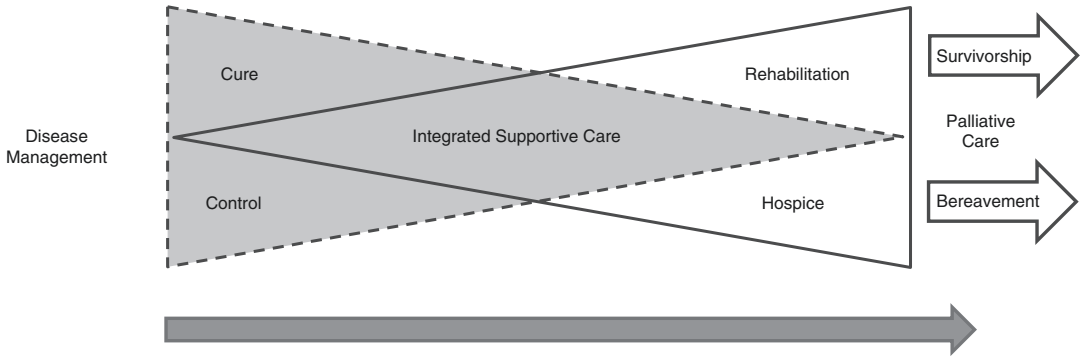

Fig. 1 The Bow Tie Model of Twenty-First Century Palliative Care, modified from Hawley P, 2014 (Hawley 2014)

6 Specialist Palliative Care

The number of specialist palliative care physicians, nurses, social workers, pharmacists, physiotherapists, music therapists, art therapists and other professionals is totally inadequate for even a minority of patients who are living with serious chronic illness to be able to access specialty palliative care services, and never will be, given that about 90% of us will die from a chronic illness and will have plenty of time to see death coming. A palliative approach to care has to be able to be provided by family doctors and specialists in all other areas of medicine in order to meet the majority of patients' and their families' needs. The specialist services need to be able to target their care to those who have the most complex needs or the most extreme suffering. The proportion of patients and families needing specialist palliative care will vary from place to place depending on the skills and resources available through primary care. In an ideal world, all health care professionals' training would include basic palliative care competencies, but in reality, this has yet to happen, so the threshold for specialist referral is appropriately quite variable. Recognition of when the point of unmet need occurs can be difficult, especially where there is no routine distress screening. Discretionary referral alone cannot be relied on to provide a timely and appropriate referral practice.

Triggers to refer can be activated automatically when transitions in care are documented (e.g., on detection of metastases in cancer care); or by expression of distress recognized through use of screening tools. As distress can occur at any time in the course of illness, screening should occur regularly from the time of diagnosis. Prompt referral for specialist palliative care support should be made at any time when physical, social, psychological, or spiritual unmet needs are not able to be satisfactorily resolved by the primarily caring team (which may include a variety of specialists as well as family medicine/general practice), including when the goal of disease management is curative in intent.

Patients do best by having access to both disease-modifying treatments and palliative care simultaneously, so it makes no sense to hand over all aspects of care to a service with limited resources when a referral is made. The most efficient model of care is to have the right people delivering the care at the right time that most suits the circumstances. Who is "right" may change a number of times over the course of a long illness, and palliative care professionals can most efficiently and cost-effectively share their expertise at multiple points in the illness trajectory, stepping back when not needed, ensuring ongoing care is provided by the referring team.

7 Awareness of Services

Just as many health care providers working outside a tertiary hospital environment are unaware of the procedures that interventional radiology programs can provide for patients, similarly physicians who have done little postgraduate training in settings where they have long-term clinical relationships with patients may be unfamiliar with the challenges of living with a long-term illness, deriving much of their knowledge from personal experience with family and friends rather than from formal training. The trend for residential hospices to be freestanding buildings in pleasant locations away from urban hospitals can lead to lack of awareness of their existence.

Students and residents infrequently have access to palliative care rotations, and the paucity of palliative care teaching in many medical school and residency programs make it difficult for physicians to understand what happens in a specialist palliative care setting. It is therefore important for palliative care teams to interact with their colleagues in other specialties on a regular basis, attending rounds, teaching, and participating in committee work. The same applies to specialists in procedure-based disciplines, so that mutual understanding of the important issues is shared and services can be developed optimally. This can be challenging when added to the responsibilities of professionals who are already overloaded with clinical work and needs to be taken into consideration in workforce planning and staffing models.

8 The Place of Interventional Radiology in Palliative Care

With respect to cancer pain, the World Health Organization's Pain Relief Ladder now has "Step 4" interventions, which include interventional procedures, at the top of the ladder (Fig. 2). "Procedures" include neuraxial infusions, neurolytic procedures, regional anesthetic procedures, and other interventions such as cryoablation and cementoplasty.

Many Step 4 procedures are in reality only available to a few patients, mostly those living close to tertiary referral centers. Their benefits in relief of suffering can be dramatic, and the cost-effectiveness of palliative procedures for those with the worst suffering is undeniable. For example, in a review of the first year of a Minimally Invasive Palliative Procedures case conference in Vancouver, BC (Chu et al. 2015), there were 103 referrals to the case conference, resulting in 69 procedures performed among 63 patients. Over 80% of procedures provided analgesic benefit. Pain scores fell across all categories post-procedure. Mean worst pain scores fell from 8.1 ± 1.4 to 4.6 ± 2.8 ($P < 0.001$). Patient function, mobility, and symptoms measured by the Edmonton Symptom Assessment System also improved post-procedure. The mean survival post-procedure was 200 days: plenty of time to enjoy the benefits. The documented rate of major adverse events attributable to MIPPs was only 2/69 (2.9%). Examples of patient reports before and after cementoplasty included the following:

> *"He says this has had a tremendous positive impact on his QOL..... He is now off opioids completely, having decided against medical advice to go "cold turkey" but he is now 6 weeks opioid-free and is feeling very good about it."*
> Pre-procedure: *"He is unable to do any physical activity now, having been fairly active just over a month ago. He continues to walk with the assistance of a 4-wheel walker and two sticks. His days are spent seated due to his pain and persistent bilateral foot drops, making ambulation tiring and quite challenging."*
> Post-procedure: *"I note that he [is doing] a lot of fairly heavy physical work in the form of woodwork. He is helping to construct a sunroom on the back of his home and tells me that this morning, he was ... in the basement and then carrying all the wood up and down the stairs."*

9 Practical Considerations with Interventional Radiological Palliative Procedures

The principles of palliative care need to be borne in mind throughout the process of delivery of interventional radiological palliative procedures. Technical competence alone is not enough, and neither is individual competence or commitment. A team approach is required, with everyone working together to make sure the procedure goes smoothly, from the radiologist to the residents/fellows, booking clerks, admitting physi-

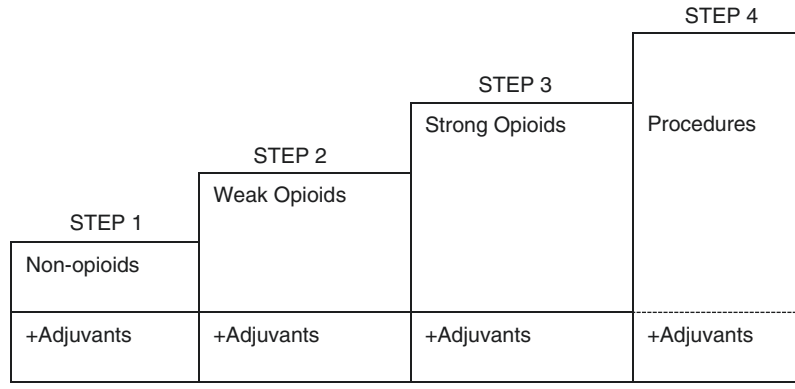

Fig. 2 The World Health Organization Pain Relief Ladder with addition of fourth step (Vargas-Schaffer 2010)

cians, nurses, anesthetists, the patient's primary physicians, and all levels of administration.

The components of an interventional radiological palliative procedures program that need to be in place can be conveniently grouped together as the "Five Cs"

- Competence
- Capacity
- Communication
- Collaboration
- Compassion

The technical competence of the interventional radiology professionals providing the service needs to be assured by proper training, supervision, and credentialing to ensure that an adequate number of practitioners with the requisite skills are available for succession planning and for a service to have adequate capacity to meet the need of the relevant population. For those patients on moderate to high doses of opioids pre-procedure, the doses of opioid need to be titrated down sufficiently rapidly to avoid sedation and respiratory depression but without causing opioid withdrawal; a skill which requires significant expertise and experience. This is particularly important for those patients taking methadone for pain because of its long half-life. Ideally, methadone should be stopped before an analgesic procedure, and an alternate short-acting opioid such as morphine or hydromorphone used instead. In reality, this is often not possible because patients on methadone for pain are usually on it because of failure to respond to or to tolerate other opioids.

The capacity of a service should be adequate to be able to provide the necessary procedures in a timely fashion. If a patient has a detailed pre-procedure assessment and then does not get a call for the procedure until some weeks later their situation may have changed, resulting in cancellations (which negatively impact the efficiency of the service) and risk of added complications when other disease-related complications have arisen, e.g., infections, thrombosis, pressure sores, pneumonia, deconditioning, opioid toxicity, and often corticosteroid toxicity. Capacity of a service requires sufficient support staff and resources to run smoothly and efficiently so that the whole system does not fall apart when one member of the team gets sick or is on holiday.

Close communication and collaboration between all people in the process are key to ensuring that patients are properly prepared for a procedure and properly cared for afterwards. Attention to symptom management, including systematic assessment and documentation, is vital. Regular case conferences will ensure that all clinicians involved in a patient's care understand the rationale for doing a procedure and what its goals are. Patients will need to move from one part of the health care system to another in order to receive specialist care, and expenses incurred in one part of the system (the tertiary referral center) will be saved in other parts of the system (acute care, home care, etc.). If these stresses are not recognized and addressed in a system-wide manner, budgetary conflict can lead to breakdown of relationships and loss of essential collaboration. Administrators, funding agencies, and medical educators need to be made aware that these skills and services need considerable expansion. The value of their investment will be seen in costs avoided as illness progresses.

Regarding the last "C"; the benefits to society of having an effective system of universal access to Step 4 of the WHO ladder are priceless. People suffering from severe pain, whether from cancer or something else, are some of the most vulnerable in society. Witnessing unrelieved suffering of someone you care for or about is a source of lifelong trauma and generates more fear of suffering in those left behind. Knowing that for at least some of them the suffering is relievable should help us strive to make palliative procedures available for all in whom noninvasive treatments are not effective.

10 Summary

Palliative care and interventional radiology are two specialties of medicine which are developing close collaborative relationships to meet the common goal of relief of pain and suffering from chronic illnesses, especially but not exclusively cancer. A mutual understanding of each other's discipline is important in delivering the best possible care to patients so that we can all live as well as possible, for as long as possible.

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Introduction to IR

Luke Lintin and Raman Uberoi

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Interventional Radiology (IR) began with an act of faith, when Charles Dotter performed the first percutaneous transluminal angioplasty (PTA) (which he originally described as "percutaneous transfemoral catheter dilation") in 1964 (Dotter and Judkins 1964). This was in the face of severe opposition from the establishment and at the time he was labelled a maverick. However, today quite rightly he is seen to be a visionary and a pioneer. He demonstrated that major surgical treatments could be done in a much less invasive and safer way. He built on the existing technologies: percutaneous selective catheter angiography using the Seldinger technique (Seldinger 1953). Although this had existed for some time prior to this, nobody up until this point had made the leap from performing diagnostic procedures to treating the disease at the same time. In its infancy, angioplasty was performed using coaxial or dilating catheters. The major problem with this technique was that the hole created in the artery had to be large (the same as the diameter that the vessel was to be dilated), limiting the size of the vessel that could be treated and resulting in a high number of complications related to the puncture site.

A German cardiologist named Andreas Grüntzig recognized the importance of angioplasty and went on to develop the first polyvinyl chloride (PVC) angioplasty balloon catheter (Gruntzig and Hopff 1974). This revolutionized PTA, as is allowed dilation to a diameter greater than the hole made in the artery. After great success using Grüntzig balloon catheters in the iliac, femoral, and popliteal vessels, Grüntzig went on to perform the first successful coronary angioplasty in 1976 (Grüntzig 1976).

Frustrated by recurrent stenosis after angioplasty, Dotter conceived, and then went on to develop the first intravascular stents in 1969 with the aim of holding the vessel open. His work on stents only made it as far as experimental studies on animals (Dotter 1969); however, there was some limited success with these which sparked the interest of other clinicians. Many of the stents that were originally developed however for use in

L. Lintin (✉) · R. Uberoi
Radiology Department, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
e-mail: Luke.lintin@nhs.net; raman.uberoi@ouh.nhs.uk

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_2

humans had complex deployment methods and required large introducing sheaths, therefore it took until the early 1980s before stenting became widespread. Stent designs were modified, and with the introduction of more robust and easier to introduce stents such as the Plamaz balloon expandable stent in 1985 (Palmaz et al. 1985) and wallstent in 1987 (Rousseau et al. 1987), stent usage gained significant popularity.

Another area of development within interventional radiology was for gastrointestinal (GI) bleeding. Early procedures were purely diagnostic, with the radiologist's sole purpose being accurately diagnosing the site of bleeding for surgeons. In 1967, Nusbaum and his colleagues discovered that low dose infusion of vasopressors directly into the mesenteric arteries was useful in reducing portal hypertension (Nusbaum et al. 1967), and this method was adopted for the treatment of acute variceal bleeds. Shortly afterwards, similar methods were developed by Rösch for the treatment of acute arterial GI bleeds, but this time using catheter-directed adrenaline infusions counteracted with systemic β-blockade (to mitigate the side effects of adrenaline) (Rösch et al. 1970). This proved successful; however, there was some concern over the risk of global gut ischemia with this method. Consequently in 1970, Rösch performed the first selective arterial embolization for GI bleeding using autologous blood clots that were infused directly into the gastroduodenal artery (Rösch et al. 1972), this became rapidly accepted as the best method for controlling acute arterial bleeding. And so came the dawn of embolization therapy. The use of autologous clots was soon replaced by surgical gelatin (Gelfoam) and glue (isobutyl 2-cyanoacrylate). Nowadays, the variety of embolic agents that are available are huge and be categorized into liquid agents (glue, ethiodol, onyx), sclerosing agents (ethanol, ethanolamine oleate, sotradecol), particulate agents (Gelfoam, polyvinyl alcohol (PVA) particles, microspheres), and mechanical occlusion devices (metallic coils and vascular plugs).

Subsequently, over the last few decades, there has been an explosion of the use of embolization techniques in a wide variety of territories including arteriovenous malformations, also to induce atrophy in benign and malignant tumors in target organs such as in the, liver, kidneys, prostate (Pisco et al. 2016), and also uterine fibroid embolization (UFE) (Pelage et al. 2000).

Transcatheter arterial embolization has also been used to reduce pain (due to neovascularization of the synovium) in osteoarthritis (OA) (Okuno et al. 2014), induce compensatory hypertrophy in the liver pre-operatively for the resection of liver tumors (portal vein embolization) and to deliver targeted radiotherapy and chemotherapy to tumors with selective internal radiation therapy (SIRT) and transarterial chemoembolization (TACE), respectively. These techniques along with different organ percutaneous ablation techniques have helped to spawn the birth of interventional oncology which is revolutionizing the treatment of cancers, particularly in the lung and liver.

In the 1980s, treatment for portal hypertension and variceal bleeding moved away from vasopressor infusions towards transjugular intrahepatic portosystemic shunts (TIPS) (Fig. 1). Several methods for creating intrahepatic shunts with long-term patency had been trialled over the years; however, it was not until Palmaz created his balloon expandable stents in 1985 that this became possible, and the first technically successful TIPS stent procedure in a human was performed in 1988 by Richter using a Palmaz stent (Richter et al. 1989).

In 1972, Dotter also pioneered the use of catheter-directed thrombolysis for the treatment of acute thrombus (that was a common complication of PTA). When recognized, a catheter was positioned within, or just next to the thrombus and an infusion of streptokinase was administered. The benefits of this were that it reduced the need for open surgery to deal with thromboocclusive complications of PTA, and that the dose of streptokinase required for local thrombolysis was significantly lower when compared to that for intravenous, systemic thrombolysis (Dotter et al. 1974) therefore reducing the risk of the treatment.

Over the years, catheter-directed thrombolysis and thrombectomy (physical removal of the

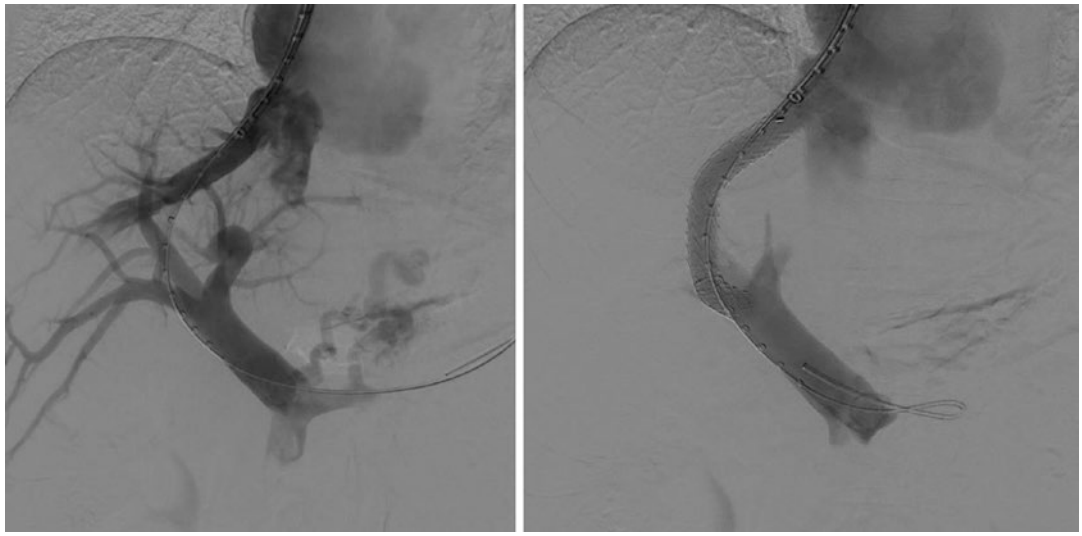

Fig. 1 A TIPS procedure performed on a 55-year-old male with recurrent bleeding from esophageal varices. The images show the placement of a stent graft between the right hepatic vein and right portal vein. *Images provided by Oxford University Hospitals NHS Foundation Trust. UK*

clot) has evolved with an ever-expanding number of pharmacological agents and mechanical devices. The scope of treatable conditions has also significantly enlarged to include the treatment of acute limb ischemia, acute central venous occlusions, pulmonary embolism, and more recently for the treatment of acute stroke. Stroke thrombolysis has already changed (and is likely to continue to evolve) to incorporate mechanical devices, in so doing dramatically reduce the procedure time, in order to salvage brain tissue. There are now many centers across the world that offer a 24-h acute stroke thrombectomy service in a similar manner to percutaneous coronary intervention (PCI) services for acute myocardial infarction.

In the 1990s, technological advances were made, combining metallic stents with non-porous, non-thrombogenic material to create stent grafts.

Stent grafts have revolutionized vascular intervention, most notably for the treatment of aneurysms and for managing cases of vessel rupture during arterial and venous endovascular procedures. In 1991, Juan Carlos Parodi published the first sentinel paper on the use of stent grafts for the treatment of aortic aneurysms (Parodi et al. 1991). Since then, endovascular aneurysm repair (EVAR) has become immensely popular and is a technique that is performed by radiologists, vascular surgeons, or as a joint procedure with both specialties. In the early years, surgical cut-down and closure of the vessels was required to perform the procedure; however, advanced in arterial closure device technology has meant that entirely percutaneous procedures are now routinely performed.

The range of devices has also considerably expanded to facilitate EVAR in patients with varying anatomy. This includes branched devices that allow the extension of the graft into the external iliac artery while keeping the internal iliac artery patent, and custom-made fenestrated grafts that maintain patency of the renal and mesenteric arteries when the aneurysm involves these vessels (Fig. 2).

Every new procedure has its complications; however in EVAR, the most common complication is endoleak (persistent arterial flow beyond the lumen of the stent graft). This has in turn led to numerous procedures, devices, and techniques being developed and utilized for re-intervention after EVAR in order to treat endoleak (the details of which will not be discussed in this chapter).

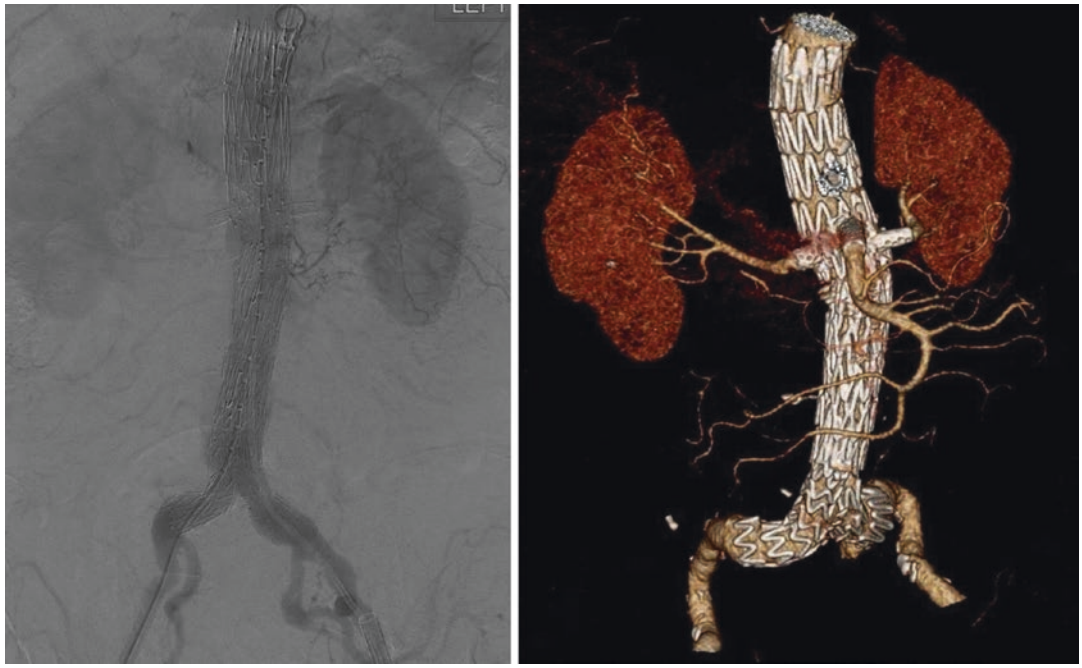

Fig. 2 Fluoroscopy image (left) and a 3D reconstruction (right) of a CT angiogram performed on a 76-year-old male who underwent elective endovascular repair of an aortic aneurysm using a fenestrated stent graft with branches into both renal arteries and the superior mesenteric artery. *Images provided by Oxford University Hospitals NHS Foundation Trust. UK*

The procedures described thus far are all achieved with venous or arterial access. However, interventional radiology has also hugely expanded in the areas of non-vascular procedures and oncology. These can be broadly categorized into urological, biliary, gastrointestinal and musculoskeletal procedures.

The first percutaneous nephrostomy was described by Willard Goodwin in 1955 who inadvertently placed a needle into the collecting system of a hydronephrotic kidney while trying to perform a renal arteriogram and then decided to leave a tube in situ in order to decompress the kidney. A technique for percutaneous nephrolithotomy (PCNL) was first described by Fernström and Johansson in 1976 (Fernström and Johansson 1976), whereby they were able to remove renal calculi via a nephrostomy tract under fluoroscopic guidance in three cases. Nowadays, with advances in the design of nephroscopes and holmium laser technology, the role of the interventional radiologist is primarily to gain access to the renal collecting system with a large (up to 30 French) sheath, through which a urologist can break up and remove the calculi under nephroscopic guidance.

The first antegrade ureteric stent was described by Arthur Smith in 1978 (Smith et al. 1978), when he described the placement of a Gibbons stent through a percutaneous nephrostomy. This technique allowed the stenting of ureters where it was not possible to insert a stent retrogradely with cystoscopy due to obscuration of the ureteric orifices (such as with large bladder tumors).

Percutaneous transabdominal cholangiography (PTC) developed popularity in the 1950s (Carter and Saypol 1952) and was for a while the gold standard method for imaging the biliary tree until advances in other imaging modalities (principally ultrasound and MRI). In the 1970s, PTC and drainage was introduced for the treatment of obstructive jaundice. Later methods were developed to cross obstructing pathologies such as stones, strictures, and tumors and stent the biliary tracts percutaneously (Fig. 3).

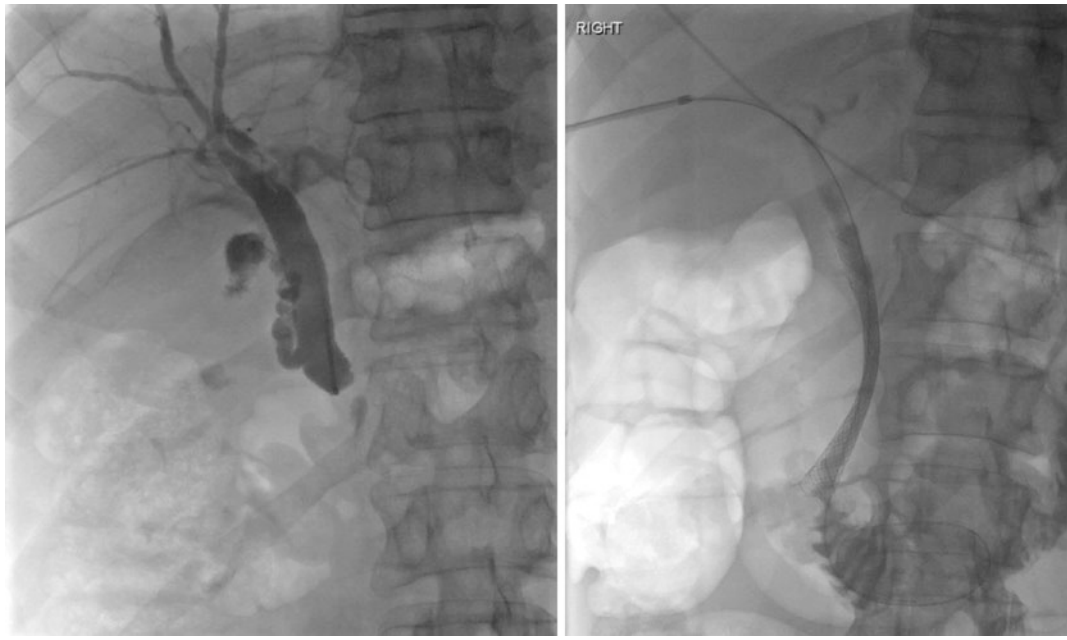

Fig. 3 Fluoroscopy images showing placement of a biliary stent for an obstructing pancreatic tumor in a 55-year-old male. *Images provided by Oxford University Hospitals NHS Foundation Trust. UK*

For the gastrointestinal system, stents have been developed to relieve obstruction due to tumors, particularly in the esophagus, duodenum, and colon as an interim procedure before surgery, or as a palliative treatment when surgery is not possible or contraindicated.

Radiologically guided techniques have also been adopted for the treatment of musculoskeletal pathology, with the mainstay of treatment including the injection of corticosteroid into joints and nerve sheaths for pain relief, and the injection of cement to stabilize osteoporotic fractures as with vertebroplasty. Image-guided ablation has also replaced open surgery for certain bone tumors with both curative and palliative intention.

Ablation is a process whereby tissue is destroyed using heating or cooling. Thermal ablation techniques include the use of radiofrequency electrical current and microwave electromagnetic energy to heat tissue, whereby cryoablation uses cooling (with liquid nitrogen or argon gas). In radiology, ablation is performed under CT or ultrasound guidance.

Ablation has been widely used for the treatment of liver tumors such as hepatocellular carcinoma and liver metastases as well as both primary and secondary lung tumors.

The main benefit of ablation is that it can avoid major surgery, when surgery to remove multiple lesions is not possible, or when the patient is not fit enough.

Advances in IR have not only been made in the instruments that are used, but also in the imaging techniques and software used to help plan and perform procedures. Commercially available technological advances made in information-communication and video games industries have significant potential applications in IR. Particularly with the use of augmented reality combined with multimodality image fusion, whereby radiologists could have access to, and manipulate relevant scans on a virtual display or even "see through" patients by overlaying three-dimensional images (acquired on the table or pre-procedure) onto the live patient's body.

It is also likely that artificial intelligence (AI) will have a role in IR. Although, as of yet it is unclear exactly how, it is likely to have a role in improving diagnosis, patient selection, or even in catheter navigation systems.

The last 50 years have truly been "the golden age" for interventional radiology, evolving from a niche interest of a few individuals, to a subspecialty that has a department in almost every western hospital. Radiologists have moved on from being "shadow gazers" to "surgeons without scalpels."

The huge rise in demand for interventional radiology is primarily due to the reduced morbidity and complication rate when compared to open surgery. The small incisions significantly reduce post-procedural pain, the length of hospital stay, and the requirement for general anesthesia, allowing treatment options in a much wider patient population.

Since its advent, Interventional radiology has moved on from being a technique employed by a small number of interested radiologists, cardiologists, and surgeons to becoming a specialty in its own right with its own dedicated training programs within radiology and also other medical and surgical fields (most notably cardiology and vascular surgery). As a result, in 2010, interventional radiology was approved as a subspecialty of clinical radiology in the UK and is now the most sought-after specialty in the United States.

However, there remain huge challenges for our fledgling specialty not least "turf wars." Many medical colleagues as well as radiologists see IRs as technicians with limited if any clinical roles and responsibility. With the relatively limited numbers of interventional radiologists, many surgical and medical specialists have begun to adopt these techniques and include them in their own specialties' operative repertoire. Probably, the best example of this is PCI: Andreas Grüntzig, inspired by the work of Dotter, performed the first successful PCI in 1977. He was described as a radiologist and cardiologist; however, now PCI is exclusively performed by cardiologists.

Vascular surgeons too have become increasingly present in the angiography room, particularly since the advent of EVAR, and many now perform the procedure in equal numbers to radiologists, and often independently.

IRs are intuitively innovators, developing new and exciting minimally invasive technologies and techniques. A common theme is that, wherever innovation in interventional radiology has led to the replacement of work offered by a particular specialty. Said specialists, whom would otherwise refer the patient to interventional radiology, may choose to learn and practice the procedure themselves, particularly if the procedure offers significant financial, resource, and patient-centered benefits.

If interventional radiologists wish to remain involved in these important, often life-saving procedures, then they must assume increasing clinical responsibility, rather than relying on referrals from other specialties. This means being appropriately trained, offering direct referrals from GPs, undertaking pre-procedural and follow-up consultation clinics, as well as being able to accommodate their patients (whether these are as day-cases or inpatients).

Radiologists have recognized this for some time, and most IR departments now have their own specialist IR nurses and healthcare assistants. In some centers, IR have their own admitting rights and dedicated IR inpatient beds (Simonetti et al. 2009).

As the repertoire and complexity of IR procedures expands, training in IR must also evolve. As with general surgery, it is inevitable that IR will follow a degree of specialization, initially into vascular and non-vascular procedures, but potentially further, particularly in large teaching hospitals and tertiary referral centers as the treatments become more specialized.

It is therefore probable that future IR trainees will require focused training in their final years in a particular subspecialty (e.g., complex vascular, biliary, urology, GI, or oncology).

Imaging remains at the heart of IR, and there will always remain close links to diagnostic and imaging techniques. But IR needs to become a dedicated specialty in its own right, with trainees choosing to specialize in IR at an earlier stage and thus gaining more years of experience in focused training as a result.

IR has evolved rapidly over the last five decades since Charles Dotters pioneering work in the 60s. It now encompasses a wide range of treatments in virtually every organ system in the body both in benign and malignant diseases. He predicted some of the potential uses and benefits of these new techniques, but even he would be astounded to see the progress that has been made. He predicted the potential turf battles and highlighted the urgent need for IRs to be clinical doctors taking overall responsibility for their patients. The next leap of faith has to come from IRs worldwide in becoming specialists in taking up this mantle and to take up more clinical responsibility, as well as continuing the evolution of these invaluable techniques, so ensuring the survival of IR for all future patients.

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Clinical Applications of Outcome Measurement

Mansha H. Khemlani

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Abstract

Palliative interventions provided by Interventional Radiology specialists have the primary intention of improving or relieving a patient's symptoms, without the direct intention to cure or prolong life. As such, the use of criterion such as survival or prolongation of life to measure the success of a palliative intervention becomes irrelevant. While technical success related to an intervention may be easier to define and measure, it does not always translate to improved patient-desired outcomes. The clinical use of outcome measurement in palliative care serves to assess the quality of care and gauge the success of interventions that are intended to improve patient symptom burden and quality of life. This chapter provides an overview to the clinical application of outcome measurement including the barriers to its use and highlights how interdisciplinary teams can incorporate them in their clinical practice.

M. H. Khemlani (✉)
Palliative and Supportive Care Services,
Department of Geriatric Medicine,
Khoo Teck Puat Hospital, Singapore, Singapore

Department of Medicine, Yong Loo Lin
School of Medicine, National University
of Singapore, Singapore, Singapore

Lee Kong Chian School of Medicine,
Singapore, Singapore
e-mail: khemlani.mansha@ktph.com.sg

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_3

1 Introduction

Palliative care patients represent a group with various diseases and symptom profiles including cancer and organ failure such as renal, cardiac, pulmonary, and neurological diseases. Each disease presents with unique symptoms which often require frequent hospitalizations and outpatient treatments. As disease progresses and care needs escalate, patients are rendered increased community or home-based palliative support, intended to reduce the burdens of scheduling and travelling to and from appointments. Palliative care is applicable early in the course of illness (Haun et al. 2017; Howie and Peppercorn 2013), alongside other therapies that are intended to prolong life such as surgery, chemotherapy, or radiotherapy. Palliative care teams function across various settings such as hospitals, hospices, and the community, inclusive of home or long-term care facilities. Although the roles of palliative care teams differ across institutions and settings, the overall goals to reduce patient symptom burden and improve quality-of-life (QOL) remain constant with the purpose of allowing patients more time and energy for the things that matter most. These goals are best achieved when patients are given individualized care that is specific to their needs.

Palliative interventions have the primary intention of improving or relieving a patient's symptoms, without the direct intention to cure or prolong life (Wancata and Hinshaw 2016). As such, the use of criterion such as survival or prolongation of life to measure the success of a palliative intervention becomes irrelevant. Appropriate interventions provided by Interventional Radiology (IR) specialists have enormous potential in providing patients with support for nutrition, alleviating symptoms such as pain, breathlessness, or discomfort from fluid retention and/or enhancing functions and QOL (Sabharwal et al. 2015). Some interventions provided by IR specialists such as transarterial chemoembolization for patients with unresectable hepatocellular carcinoma have also shown to significantly prolong survival in selected patients (Llovet and Bruix 2003). Other interventions such as percutaneous nephrostomies and biliary drainage can also alter the course of a patient's illness trajectory and prolong life, without which, patients would succumb to renal or liver failure. Interventions provided by IR specialists are often considered when traditional opioid-based therapies are inadequate to control suffering and other surgical interventions are at risk of causing unacceptable adverse effects.

Unlike some other areas of health care, palliative care takes a holistic approach giving due consideration to psychological, social, and spiritual dimensions in addition to its efforts in alleviating physical suffering (World Health Organization n.d.-a). Consideration of these additional dimensions, however, can make it challenging to assess concepts such as suffering. Whilst technical success related to an intervention, such as successful placement of a tube or drain, may be easier to define and measure, it may not always translate to improved patient desired outcomes. The interdisciplinary team, with their expertise in evidence-based medicine and disease management, should involve the patient and the family members, who are experts in the lived experience, in deciding on the intended goals of the intervention on offer. These goals should be matched with the patient's values and wishes and must be built upon open, honest communication between the interdisciplinary team and the patient.

2 Why Do We Need Outcome Measures?

An outcome can be described as the "change in health status or quality of life attributable to health care" (Bausewein et al. n.d.). Outcome measurement starts with a measure of the patient's baseline health status and then assesses changes against that baseline (Greenhalgh et al. 1998). In simpler terms, outcome measurement allows clinical teams to gauge changes in a patient's health over time. In health care, outcome measurement serves three main purposes which are outlined below.

Clinical Use: In palliative care, there has been an increase in demand for outcome measurements, especially patient-reported outcome measures (PROMs) (Bausewein et al. n.d.; Bausewein et al. 2011), to assess the quality of care and gauge the success of interventions that are intended to improve patient symptom burden and QOL. As health care outcomes are directly related to the patient's experience, PROMs consider the patient's perspective in the evaluation of interventions. As such, it is the patient, not the interdisciplinary team nor the patient's family, who primarily provides information regarding changes in symptom burden and/or QOL. To ensure this, patients must be able to self-complete the necessary instruments. With health care professionals' accountability to patients and the increasing focus on patient autonomy, PROMs position patients at the center of care and help interdisciplinary teams focus on what matters to patients and families. Analyzing the change in PROMs pre-intervention and post-intervention helps both the patient and the team appreciate the amount of change that has occurred in the patient's symptom burden or QOL as a result of the specific intervention. Without consensus on meaningful individual outcome measures, evaluation of the risks and benefits for specific interventions will not be possible.

Funding and Resource Allocation (Gomes et al. 2009; Hessel 2008): Other than the use of outcome measures to analyze and monitor clinically relevant outcomes in palliative care, there has been increasing focus on health care economics to evaluate both the input and the output. Health care institutes and service providers are held increasingly accountable for the appropriate allocation of finite resources and to verify that patients are receiving the best possible care in relation to these resources. With increased emphasis on equitable service delivery and value-driven outcomes, it becomes imperative for service providers and funding agencies to demonstrate effectiveness alongside value for money, to continue funding support.

Audit, Accreditation, and Benchmarking: In addition to demonstrating effectiveness for funding purposes, greater accountability is demanded by national accreditation agencies prompting organizations to adopt transparent and more formalized approaches to outcome measurement. Advances in the field of palliative care can only be achieved through comparisons of intervention outcomes on a national and international level and to use this research to improve patient and family outcomes and reduce variation across organizations. The Australian Palliative Care Outcomes Collaboration (Clapham and Holloway 2018) (PCOC) (www.pcoc.org.au) is one such voluntary program that is improving the quality and outcomes of palliative care.

3 What Outcome Measures Should We Use?

There are a number of outcome measures for use in palliative care which differ in the domains and dimensions they measure, making it difficult for health care professionals to decide which to choose. Outcome measures differ in their accessibility, feasibility, length, and even cost. At the heart of palliative care lies the concept of quality of life which includes physical, psychological, social, and spiritual aspects of a patient's experience. As no one individual or discipline can fully address all of these, comprehensive palliative care requires an interdisciplinary team. Along with open and transparent discussions about realistic goals for the intervention, interdisciplinary teams also need to decide what data to collect, for what purposes and by whom. Whilst there is a lack of widely accepted standards for outcome measurement, the choice of outcome measure will be dictated by the setting and dimensions a team intends to measure, for example, individual patient symptoms, quality of life or both.

3.1 Patient-Reported Outcome Measures (PROMs)

PROMs are holistic in that they measure a patient's subjective perception of symptoms alongside other social, psychological, and spiritual aspects. They are regarded as the "gold

standard" in palliative care (Bausewein et al. 2016). To prevent burdening the patient with *respondent fatigue* (Ben-Nun 2008) and/or *respondent burden* (Graf 2008), and to be able to add value to a patient's care, PROMs should be sufficiently brief and straightforward with careful consideration given to the types of questions and items that are required to measure outcomes. PROMs can be captured using a variety of standardized and validated instruments. Many of these have been developed for the assessment of treatment or intervention effectiveness. Even with the use of brief instruments, cognitive impairment and deterioration during the dying phase can make PROMs challenging to use. The challenges associated with PROMs are elaborated upon in the section "Challenges and Barriers to using outcome measures."

Symptom assessment: Symptom-specific measures can be used to measure detailed physical symptoms such as pain or breathlessness. To illustrate using the example of an intervention intended to alleviate pain such a nerve block, the patient's pain can be assessed by means of either unidimensional scales such as the Visual Analogue Scale (VAS) (Ingham et al. 2015), the Numerical Rating Scale (NRS) (Ingham et al. 2015) or the Verbal Descriptor Scale (VDS) (Gagliese and Melzack 1997), or as part of multidimensional scales such as the McGill Pain Questionnaire (Melzack 1975) and the Brief Pain Inventory (Daut et al. 1983). With such measures, the pre-requisite is to establish the patient's baseline symptoms and repeat the measure post-intervention to monitor changes over time. A repeated measures approach is useful in assessing the effectiveness of an intervention as it provides important information regarding a specific patient's illness trajectory over time.

Quality-of-Life (QOL) assessment: Palliative interventions done by IR specialists can reduce symptom burden, thereby improving QOL for patients (Monsky et al. 2009). The World Health Organization defines QOL as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (World Health Organization n.d.-b). Although both the 15-item European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Palliative Care (QLQ-C15-PAL) (Groenvold et al. 2006) and the 17-item McGill Quality of Life Questionnaire (MQOL) (Robin Cohen et al. 1995) incorporate one global QOL item, the QLQ-C15-PAL lacks measures of existential and spiritual issues. Whilst the QLQ-C15-PAL enquires about the patient's symptoms and function over the last 1 week, the MQOL has a time frame of 2 days.

3.2 Other Patient-Centric Outcomes

Patient satisfaction with the decision-making process: There exists significant uncertainty with regard to patient outcomes in relation to palliative interventions. This stems from the multimorbidity especially in older adults as well as a dearth of quality evidence for outcome measures related to palliative interventions. Other than outcome measures, one approach would be to assess the processes of care itself. The CollaboRATE (Elwyn et al. 2013) is a brief instrument that measures patients' perceived engagement in the shared decision-making process in the context of their clinical care. It serves as a valuable indicator of patients' involvement in their treatment and asks three questions of patients: How much effort was made to help you understand your health issues? How much effort was made to listen to the things that matter most to you about your health issues? How much effort was made to include what matters most to you in choosing what to do next?

Burdens from the intervention for the patient: The experience of a palliative patient is marked not only by the symptoms from the underlying life limiting illness but also by the interventions and treatments the patient is subject to. Although the incidence of morbidity and mortality from many routine interventions performed in interventional radiology suites is much lower than that of surgery because of its minimally invasive nature, complications still do occur (Savader

et al. 1993). Complications can be classified into three groups depending on their temporal relation (Tapping et al. 2012) to the intervention: immediate complications occur less than 24 h from the procedure such as pain, breathlessness, leakage from puncture site, and discomfort; early complications occur between 24 h and 30 days from the procedure such as puncture site infection, tube dislodgement, or temporary occlusion of tubes or drains; and late complications that generally occur after 30 days from the procedure such as persistent pain or discomfort, incisional hernias, tube dislodgement, or subcutaneous tumor growth. As some of these complications only become apparent weeks or even months after an intervention, this warrants longer term follow-up for patients. Patients are usually managed by their primary physicians after the intervention, and these physicians may not always have an in-depth knowledge regarding the intervention and possible late complications. It is important for the interdisciplinary team to share knowledge and information regarding the potential complications that may occur after a specific procedure to allow for care continuity and accountability. The Cardiovascular and Interventional Society of Europe (CIRSE) set up a task force to produce a three section checklist for IR (CIRSE IR Patient Safety Checklist) (Lee et al. 2012) with an aim to reduce the incidence of complications after IR procedures. If patients or proxies assert that the perceived burden of an intervention outweighs the potential benefit or effectiveness of the intervention on offer, the intervention should be abandoned or discontinued whenever possible.

3.3 Burdens on the Caregiver

The term "caregiver" is used synonymously with the term "carer." The National Institute of Clinical Excellence (NICE), in their 2004 report "Guidance on cancer services improving supportive and palliative care for adults with cancer," define "caregivers" as "lay people in a close supportive role who share in the illness experience of the patient and who undertake vital care work and emotion management" (National Institute for Clinical Excellence 2004). Caregivers may include people not related by blood or legal ties. They may be geographically dispersed, and not necessarily confined to the same household as the patient. Caregivers may include blood-related family, extended family, friends, or even neighbors. There is often a burden placed on family and caregivers who have their own personal, social, emotional, and financial needs to look out for whilst caring for someone who requires palliative care (De Korte-Verhoef et al. 2014). As disease progresses, the patient's ability to self-care and manage tubes and drains becomes compromised. It may then become necessary for the informal caregivers to take on this added burden. Alongside the impact of interventions on patients, we need to also measure the potential impact they have on family and caregivers and assess their ability to cope. For example, whilst tunneled catheters have allowed fluid removal, resulting in improved QOL from reduced symptom burden (Monsky et al. 2009), to be performed from the comfort of the patient's own home, their unpaid caregivers are often faced with the daunting tasks of managing tubes and drains if patients are unable to self-care. How does the intervention impact the informal caregiver, in terms of increased burden of care, financial strain, and emotional stress? Some outcome measures, such as the Zarit Burden Inventory (ZBI) (Zarit et al. 1980), specifically look at the needs and experiences of caregivers in relation to how they manage their responsibilities to the patient as well as themselves. Whilst the ZBI was originally designed for caregivers of dementia patients, the shorter 12-item and 6-item versions have since been validated and used in patients with advanced cancer and other advanced illnesses in palliative care (Higginson et al. 2010).

3.4 Cost Savings and Facilitating Transitions of Care

There is increasing evidence that procedures offered by IR specialists are safe, effective and result in cost savings compared with surgical techniques. A Canadian report (Baerlocher 2007)

suggests that $180.3 million in direct health care costs could be saved annually if IR procedures replaced existing surgical treatments for eight diseases, in appropriate circumstances.

As disease progresses, or simply due to the chronicity of certain diseases, some patients require repeated visits to the hospital for serial paracentesis or thoracocentesis to provide relief from symptoms such as pain or breathlessness. As previously mentioned, interventions such as drain placements, including tunneled catheters, allow fluid removal to be performed in a patient's home. The palliative care team within the hospital or community can assess the patients' self-care abilities and/or identify caregivers who are able and willing to assist and provide them with the specific information and training necessary to translate these interventions to improved symptom relief and improved QOL in their own homes. Ideally, the specific education and training should begin early, giving both the patient and their informal caregivers sufficient time to adjust and adapt. This support helps alleviate the stress and the burden of frequent hospital visits.

Often such interventions are not available once a patient, in the advanced stages of the disease, makes the transition to hospice care. By providing these patients with such specialized care, IR specialists help create a smooth transition from hospital-based palliative care to hospice care with the necessary interventions to keep patients comfortable and improve QOL in their last days.

4 Choosing the Right Measures

Since outcome measures in palliative care can vary across aspects of ease of use, length, measurement window, accessibility and cost, it can make the selection of a single outcome measure for clinical use challenging.

It therefore becomes necessary for the interdisciplinary team to establish a clear goal in selecting one outcome measure over another. It is recommended by the European Association for Palliative Care (EAPC) Task Force on Outcome Measurement (Bausewein et al. 2016) that outcome measures are selected based on their relevance to the clinical task being delivered, the aims of the intervention and the population under consideration. Whilst single item measures, such as the NRS or VAS, are easier to interpret than multi-item measures, multi-item measures have the advantage of a more in-depth assessment (McDowell 2006) of a patient's experience.

A balance between single item and multiple item measures may be necessary. For example, multiple item tools can be completed through add-on single item measures. This approach ensures that problematic areas are investigated further and that benefits of single and multiple item measures are optimized.

4.1 Requirements for Good Outcome Measures in Clinical Care (Greenhalgh et al. 1998)

When choosing a measure, clinicians should select instruments that are both reliable and valid in palliative care. The *reliability* (Higginson and Harding 2007) of an outcome measure refers to consistency in measurement over time (i.e., the reproducibility of same or similar results under unchanged conditions). A value is assigned, usually a correlation coefficient between 0 and 1; the higher the correlation coefficient, the higher the reliability. The threshold for acceptable reliability is generally 0.8 (Granda-Cameron et al. 2007). *Validity* (Higginson and Harding 2007) refers to how well an instrument is measuring what it should be. A balance must be achieved between good psychometric properties and feasibility for routine clinical use (Greenhalgh et al. 1998). Measures that are easy to use clinically but are not validated should be approached cautiously as there is no guarantee that they accurately assess what the team intends to measure.

Instruments are also selected for their *appropriateness* and *acceptability* (Higginson and Harding 2007) for routine clinical use including the ease of application, length of instrument and time required for completion and its

responsiveness to change. *Responsiveness to change* refers to "whether the measure can detect clinically important changes over time that are related to the course of the disease or to an intervention, such as symptom management" (Higginson and Harding 2007). When evaluating culturally diverse populations, the interdisciplinary team must also take into account the availability of instruments in multiple languages and cultural variations.

Additionally, a patient's place of care may change as their health condition declines and their needs change. Using measures that allow for comparisons across palliative care settings aids care coordination, communication between providers and seamless transitions between care settings such as the acute hospital, community, and hospices. Therefore, it is recommended that the interdisciplinary team use measures that can be applied across various care settings. For example, the Palliative Care Outcome Scale (POS) (www.pos-pal.org) has been validated in several settings including hospitals, the community, nursing homes, and hospices (Hearn and Higginson 1999).

5 Barriers to Using Outcome Measures in Clinical Care

Some of the challenges in using outcome measures for clinical purposes are concerns about patient burden from the use of measures that are too long or time-consuming, poor accessibility and costs related to the use of the measure, and the lack of training and guidance for staff on how to use the outcome measurement.

Challenges with PROMs: PROMs may become increasingly challenging to use as patients undergo changes in their cognitive or physical abilities, their ability to communicate and/or alterations to their conscious states as disease progresses or as death nears. Patients with cognitive or communication deficits can have pain behaviors like grimacing, moaning, guarding, social withdrawal, irritability, or aggressiveness (AGS Panel on Persistent Pain in Older Persons 2002), some of which can be quantified with validated tools (Herr et al. 2011). Observing individual changes in these behaviors in response to interventions are some of the most reliable behavioral indicators of pain. Alternatively, if patients are unable to answer the questionnaire, consideration should be given to allow for proxy reports; proxies such as relatives or health care providers can be used to fill in the measures as an alternative source of information. Proxy reports may be helpful as family members and others close to the patient can provide valuable insight into changes that may be occurring. However, the evidence about the accuracy of proxy ratings is conflicting, and there has been debate about how accurate these ratings are and how much they reflect patients' views. Compared to patient's self-reports, physicians have shown to underestimate the severity of patients' symptoms such as pain and breathlessness, as well as patients' QOL (Nekolaichuk et al. 1999; Jones et al. 2011). Similarly, caregivers have also shown bias in underestimating QOL compared with patients' self-report (Jones et al. 2011).

Challenges for use of outcome measures in different communities: Outcome measures may need to be adapted based on differing cultures and languages. The challenge is ensuring that the measures portray the same meaning and demonstrate the same impact across different communities. This can be accomplished by taking into consideration cultural differences in translation for palliative care use (Dunckley et al. 2003; Eisenchlas et al. 2008).

6 Getting Started with Outcome Measurement

For many health care professionals, core clinical training may not have addressed the need for routine integration of outcome measurement within their practice. In order to overcome this challenge, teams need to clearly establish the value of outcome measurement to patient care. If outcome measures provide significant information that adds value to the management of patients, the task of collecting such data will be perceived as less burdensome (Greenhalgh et al. 1998).

As a start, clinicians need to be trained on what measurement instruments to use, how and when to use them. Once the patient and the interdisciplinary team have decided on the intended goals of a particular intervention, a potentially appropriate measure is to be identified. The clinical team should then consider to pilot the instrument on a small group of patients. This pilot can help ascertain the feasibility and appropriateness of that measure. As outcome measures require multiple assessments, set against a baseline, clinical teams also need to decide on predetermined time points at which data is to be collected. These predetermined time points should be the same for all patients in relation to the same intervention (Dawson et al. 2010). Teams need to decide on who will collect this information and where it will be recorded. If data is collected with the intention to assess the clinical effectiveness of an intervention, the completed outcome measures need to go into the patient's records and shared amongst the interdisciplinary team. Ensuring that outcome measures are provided to the Intervention Radiology specialist helps in evaluating the effectiveness of interventions. Finally, to reduce the add-on burden of outcome measurement perceived by clinicians, it is important that outcome measures become strongly embedded within the system and structures at an organizational level so that clinicians incorporate appropriate outcome measures without a second thought.

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Ethics, Consent, and Communication Challenges

Chua Zi'en Ruth, Pijush Sarker, and Mansha H. Khemlani

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Abstract

Palliative care is an approach that strives to improve the quality of life for patients and their families facing life-threatening illnesses. Through the appropriate usage of minimally invasive, image-guided procedures, the interventional radiologist can significantly improve both symptoms and quality of life for this group of patients. As with all practicing clinicians, interventional radiologists have ethical responsibilities to not only their patients but also to themselves, other healthcare professionals and society at large. In this chapter, we highlight several ethical issues and communication challenges that may arise when such procedures are considered for patients with a limited life expectancy. These include the use of potentially inappropriate or medically futile therapies, shared decision making, decision-making capacity, and the importance of informed consent.

C. Zi'en Ruth (✉) · P. Sarker · M. H. Khemlani
Palliative and Supportive Care Services, Department of Geriatric Medicine, Khoo Teck Puat Hospital, Singapore, Singapore

Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

Lee Kong Chian School of Medicine, Singapore, Singapore
e-mail: chua.ruth.z@ktph.com.sg

1 Introduction

The field of interventional radiology is one that is relatively young and rapidly evolving. Under image guidance, intervention radiology (IR) specialists are able to perform minimally invasive diagnostic and therapeutic procedures for a large

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_4

variety of medical conditions. Several of these have largely replaced more invasive and riskier surgical alternatives, while others offer completely new therapeutic options. When cure is no longer a possibility, the option of a palliative intervention to reduce the physical symptom burden is the next best alternative. The IR specialist makes a significant contribution in the improvement of symptoms and quality of life in the palliative care population.

In this chapter, we highlight several ethical and communication issues that may be especially relevant to this particular group of patients.

2 Medical Futility at the End of Life

Caring for patients in the late stages of a life-limiting illness is a challenging experience for all those involved. In particular, ethical dilemmas may arise when patients, families, and their physicians disagree about whether a treatment is harmful, or even medically "futile." When the patient is incompetent, or unable to express their wishes with regard to treatment, families themselves may fracture over differences in opinion or over pre-existing familial conflicts, thus further clouding the decision-making process.

The idea of medical futility has its roots in antiquity, with Hippocrates himself entreating physicians to avoid treating those "overmastered by their disease." Derived from the Latin word "futilitis," or "leaky," a futile action is akin to trying to fill a leaking jar. In essence, Hippocrates counsels fellow physicians not to provide treatments that will not work, no matter how often it is attempted. Despite its ancient origins, medical futility has proven difficult to define with a variety of definitions based on physiological, qualitative, and quantitative paradigms (Brody and Halevy 1995).

Physiological futility is where the proposed intervention cannot physiologically achieve the desired outcome. It is seen as the most objective form of futility and requires that a medical intervention results in a specific physiological goal. Quantitative futility, however, focuses on the likelihood that a proposed intervention will achieve the desired effect. Qualitative futility is when the proposed intervention results in an outcome so poor that it would have been better to not have proceeded at all. This difficulty in clearly defining medical futility illustrates a key point; medical futility cannot simply be seen as a nebulous free-floating concept; it must be tied to a specific goal. Endeavoring to solely preserve organ or physiological function alone also invariably disregards patient or family-centric goals of care.

On a practical level, it may also be advisable for physicians to avoid using the term "futile" when speaking to patients or their families. Patients and their families may interpret this to mean that the healthcare team has given up on the patient altogether and that nothing else can be done. As the old aphorism goes "To cure sometimes, to relieve often, to comfort always," there is always something more that can be done for patients as healthcare professionals strive to relieve their suffering. It may also be better for physicians themselves to view interventions as "potentially inappropriate in the given context," rather than "futile." This acknowledges that the treatment or intervention may at least have some chance of achieving the hoped for outcome; however, competing ethical principles (such as non-maleficence and justice) would justify the non-provision of the above.

3 Shared Decision-Making at the End of Life

The concept of patient autonomy has been one of the most important developments in medical ethics. In the past, physicians often favored a more paternalistic approach, where medical decisions were made with no or little input from patients or their families. Since then, there has been a modern paradigm shift towards shared decision-making, where the importance of the patient's autonomy is upheld (Brock 1991). In this model, determining the most suitable intervention for a patient involves a collaborative decision-making process between the interdisciplinary team and

the patient (Barner and Hromadik 2020). The concept of shared decision-making thus involves taking into account both the best available evidence and the patient's values and preferences to reach an agreed upon decision (Belanger 2017).

First and foremost, we must consider what interventions can realistically be offered to the patient, given the circumstances and the available expertise. Members of the interdisciplinary team also need to be in agreement about the appropriateness of the intervention on offer.

In addition, it is important that the patient is part of the decision-making process and provides informed consent for the selected intervention. As such, we need to consider a patient's goals, values, and preferences when deciding on a course of action. This allows the maximization of beneficial outcomes (concept of *beneficence*) while limiting harm (concept of *non-maleficence*) (Olsen et al. 2010). In doing so, we would need to consider factors including the aggressiveness of the patient's disease, expectations of treatment and outcomes, symptom burden, anatomy, comorbid conditions, and the patient's history in responding to similar interventions (Arnstein 2018).

Although interventional radiological procedures are generally minimally invasive, complications are still an unavoidable consequence of medical practice. This may be especially relevant for a relatively new specialty known for pushing the frontiers of modern medicine. As such, intervention radiology procedures should never be undertaken without a proper medical indication. This may seem obvious, but there may be instances in which medical judgment may be clouded by external pressures. These pressures include a family or patient's insistence to "do something" or the desire to try a new therapeutic intervention or device.

Another key consideration is that of the patient's overall prognosis; an intervention unlikely to alleviate the symptoms within a reasonable time frame should not be offered. Although multiple prognostication tools have been developed, accurate prognostication remains challenging and often fraught with inaccuracy. As a general rule of thumb, observing factors such as the stage of the cancer, the overall disease burden, response to oncological therapy and the patient's functional status can aid us in obtaining a more accurate prognosis to guide us in selecting an appropriate intervention. The Eastern Cooperative Oncology Group (ECOG) Performance status (Karnofsky and Burchenal 1949), the Karnofsky Performance Status (KPS) (Zubrod et al. 1960), and the Palliative Performance Scale (PPS) (Anderson et al. 1996) are all some of the frequently used tools that can be used to assess a palliative patient's functional status.

It is also crucial to consider the patient for whom the intervention may cause more harm than good. In particular, the potential impact of any complication(s) for patients at the end of life is often more significant, compared to patients with a longer life expectancy. These patients are often frail, with much less physiological reserve to recover should they suffer peri-procedural complications. Serious adverse events such as visceral perforation following a percutaneous gastrostomy, while rare, may still occur with devastating consequences. Even if the patient recovers, any time lost is often precious and may result in a patient missing a significant personal event such as a wedding or one last family vacation. An unexpected complication may also hasten a patient's already declining functional status, ultimately leading to a patient spending his or her remaining time in an acute hospital setting.

There are several challenges in shared decision-making. In involving the patient in the decision-making process, the team needs to be aware that these decisions can be highly emotional and thus must be handled with great sensitivity. Another challenge arises with the assumption that patients would need clear and precise information about their conditions and prognoses to aid in the decision-making process (Belanger 2017). However, providing this information may decrease their hope, which is crucial in palliative care (Kirk et al. 2004). Finally, it can be a challenge to involve patients in the decision-making process when there is so much uncertainty regarding the patient's outcomes. This uncertainty stems from the fact that the health

problems encountered in palliative populations, especially amongst older adults, can be complex. In addition, when it comes to palliative patients, there is insufficient evidence to provide precise information regarding the expected outcomes of interventions (Belanger 2017). With all this uncertainty, it can prove challenging to provide patients with the information they need to make informed decisions.

Despite these difficulties, it is the authors' belief that the key to overcoming some of these challenges involves open and honest communication between the patient, their family, and the interdisciplinary team.

4 Decision-Making Capacity

The capacity to make one's own decisions is fundamental to the ethical principle of respect for autonomy. It is also a key component in obtaining informed consent. All practicable steps need to be taken to help a person make their own decision. While assessing capacity, treating physicians need to assume that a person has capacity until proven otherwise. Unfortunately, it is not uncommon for patients to experience cognitive decline and reduced consciousness as they approach the end of life, thereby impacting their decision-making capacity. As a general principle, a person is deemed to be lacking capacity if he or she is unable to understand, remember, weigh, or rationalize the information and communicate his or her decision consistently.

Much like the concept of futility, decision-making capacity must be linked to a specific goal. Clinicians must remember that decision-making capacity is both time and decision specific. Therefore, the same patient may have the capacity to decide on the preferred place of care, but lack the capacity to understand a complex surgical procedure. A person's age, appearance, or aspect of behavior are also not determinants of the decision-making capacity. Each assessment must thus be based on its own merits. As an exercise of his or her own autonomy, a mentally competent person can also choose to nominate his family members to make decisions on his or her behalf. It may also be more common in certain cultures to have joint decisions made as a consensus by the patient in consultation with other family members (Fan 1997). If, however the patient in question is unable to make decisions regarding his or her care, it stands to reason that decisions must be made on their behalf.

Several ethicists have described a standard, stepwise approach that is based on the principle of autonomy (Emanuel and Emanuel 1992). First, advanced directives are examined. If none are available, substituted judgement is often invoked, asking "what the person would have wanted," based for example on past preferences that were previously expressed. If no information about the patient's prior wishes are available, however, the principle of best interest is used. This requires a decision to be made by objectively considering what is beneficial to the person lacking capacity.

The principle of best interest arose from the Mental Capacity Act embedded in English law (Mental Capacity Act 2005). The authors are cognizant that our readers practice across different legalizations, however, we believe the principle serves as a good guide for all healthcare professionals. In short, best interest decisions should promote the person's welfare in a manner with the least constraints to their liberty. Best interest decisions are not to be made out of convenience and healthcare teams making these decisions must be mindful to include both medical and non-medical considerations, such as what was known about the patient's previously expressed values, preferences, and wishes. Certain courts (such as under English law) do allow an appointee to make decisions, if the person in question loses mental capacity in the future. Again, we would urge our readers to familiarize themselves with the legal system and settings that they practice in.

5 Informed Consent

Radiologists traditionally have not placed much emphasis on the consensual aspects of medicine. Although mitigating the risks of patient exposure

to radiation and contrast mediums generally does fall under the purview of radiologists, the primary responsibility for patient care, including all diagnostic imaging that the patient was submitted to, still lies with that of the referring clinician. With interventional radiology introducing a surgical dimension to the specialty, the onus of responsibility for informed consent has now slowly shifted. IR specialists must thus take considerable care to ensure that the patient fully understands the procedure that he or she is consenting to. Significant differences in medical, public, and legal procedures towards informed consent exist across different healthcare settings. As such, there is no "right" way to obtain informed consent, and it would be impossible to cover all aspects across various jurisdictions in this chapter. It may be helpful however, to consider general principles, which should serve the IR specialist in good stead.

In essence, informed consent is about the patient having sufficient information to make a medical decision. It is a fundamental element of all interactions between a physician and the patient. It is also part of the physician's overall duty of care to his or her patients. Obtaining informed consent for an intervention or treatment broadly entails the following: discussing the details of the proposed treatment, additional interventions that might be required, both common and the not-so-common but serious side-effects, the probability of success and any alternative treatment options.

Open and honest communication between the IR specialist and the patient is paramount. If possible, arrangements should be made for the IR specialist to speak to the patient prior to the procedure itself. This should ideally be done before the procedure itself is scheduled and should preferably occur in a setting away from the radiology suite. This allows ample time for the IR specialist to carefully explain the nature of the procedure and the proposed benefit and risks involved. It also gives the patient the time and the space to reflect on what has been discussed before the procedure is arranged. If necessary, the patient can also clarify his or her concerns and discuss alternative options with the primary physician. It would also be prudent for this consultation to be undertaken by the IR specialist who is going to carry out the procedure. If delegation is necessary, this task must be done by an individual who is equally adept at explaining the procedure and addressing any reservations that the patient may have.

During the consultation, the patient must be counseled with regard to common or significant risks involved. As with most things in life, a patient's understanding of medical risks is not entirely objective. How individuals perceive risk is often influenced by multiple factors; for example, a patient's gender, prior beliefs, and past experiences can often impact decision-making (Hallowell et al. 1997). How the risk information itself is conveyed will also influence a patient's perception of risk; a cognitive bias known as the "framing effect" (Plous 1993). For example, a patient is more likely to agree to a proposed intervention if it is framed in a more positive light: 90% chance of survival vs. 10% chance of death. Patients are more likely to perceive the later as more hazardous, despite both numbers describing identical risk. The amount of detail the IR specialist is expected to share with patients often varies between medico-legal systems and is highly dependent on individual patient preferences. It would thus be prudent for the IR specialist to familiarize him or herself with the medico-legal requirements in his or her chosen country or state.

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Intravenous Access Solutions

Rahul Lohan and Kabilan Chokkapan

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1 Introduction

A well-planned venous access is quintessential in managing the physical needs of terminally ill patients. Oral administration of medications is often difficult in these patients secondary to progressive dysphagia, nausea, vomiting, and intestinal obstruction. The subcutaneous route usually serves as the initial parenteral route due to its ease of use and wide availability. However, when subcutaneous administration is suboptimal or impossible, the patients require intravenous routes to administer high-dose opioids, palliative chemotherapy, maintenance fluids, blood components, and total parenteral nutrition (Gallieni et al. 2008).

The venous access devices (VADs) are categorized into peripherally inserted central catheters

R. Lohan (✉) · K. Chokkapan
Department of Diagnostic Radiology, Khoo Teck Puat Hospital, Yishun Central, Singapore, Singapore
e-mail: lohan.rahul@ktph.com.sg

© Springer Nature Switzerland AG 2021

P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_5

Table 1 Types of intravenous access

	Expected duration	Ideal setting	Main advantage	Main disadvantage
Short-term access				
– Short peripheral cannula – Central venous catheters – PICC	3–7 days 1–3 weeks 1–6 weeks	Inpatient, Inpatient, Inpatient as well as outpatient	Ease of insertion Low cost Low risk at insertion	Short duration High risk of catheter related blood stream infections (CRBSI)
Intermediate duration access				
– Tunnelled catheters (Hickman, Broviac)	Up to 6 months	Outpatient	Lower risk of CRBSI	High cost
Long-term access				
– Subcutaneous ports	Months to years	Outpatient	Indefinite duration	High cost

(PICC), non-tunnelled central venous catheters, tunnelled catheters with anchoring cuff and implanted ports. The length of therapy and frequency of venous access guide the choice of venous access device (Gallieni et al. 2008) (Table 1). Patients' perferences certainly play an important role. PICCs and non-tunelled catheters are used for frequent (daily) access over a short time frame. Tunnelled CVCs are preferred for intermediate duration, and long-term intermittent usage often requires creation of subcutaneous ports.

2 Peripherally Inserted Central Catheters (PICCs) and Non-tunnelled Central Venous Catheters

2.1 Indications and Contraindications

PICCs are small-bore catheters placed through a peripheral vein in the arm or leg, whereas the non-tunnelled CVCs are inserted more proximally via an internal jugular (IJ), subclavian, or femoral venous access. These are used for short-term (<2–4 weeks) infusion and parenteral nutrition therapy (Gallieni et al. 2008).

The indications for placement of these catheters include (1) hydration when patient prefers an intravenous to a subcutaneous route (2) total parenteral nutrition, (3) administration of medication, particularly high-dose steroids and palliative chemotherapeutic drugs, (4) active infection or coagulopathy that prevents placement of a tunelled central venous catheter or subcutaneous port (Yamada et al. 2010).

There are barely any contraindications to PICC and non-tunnelled CVC placement. These catheters can be safely inserted despite existing coagulopathy, thrombocytopenia, or active infection/bacteremia. PICCs should be avoided on the same side as previous mastectomy, axillary lymph node dissection, focal infection, or radiation injury.

2.2 Patient Preparation

Ultrasound examination of insertion site is performed to confirm the patency of target vein. An international normalized ratio (INR) of 2.0 or less with a platelet count of 50,000 is preferred. However, if the INR or platelet count cannot be reasonably corrected in time and the clinical situation warrants an immediate access, a central line can be placed without significant complications. Aspirin and Clopidogrel need not be withheld. Low molecular weight heparin should ideally be withheld for 1 dose before the anticipated procedure.

2.3 Technique

2.3.1 Peripherally Inserted Central Catheter

A tourniquet is placed at the proximal arm to distend peripheral veins. The basilic vein in distal arm is the favored access site (Fig. 1). More central a location closer to axilla increases the

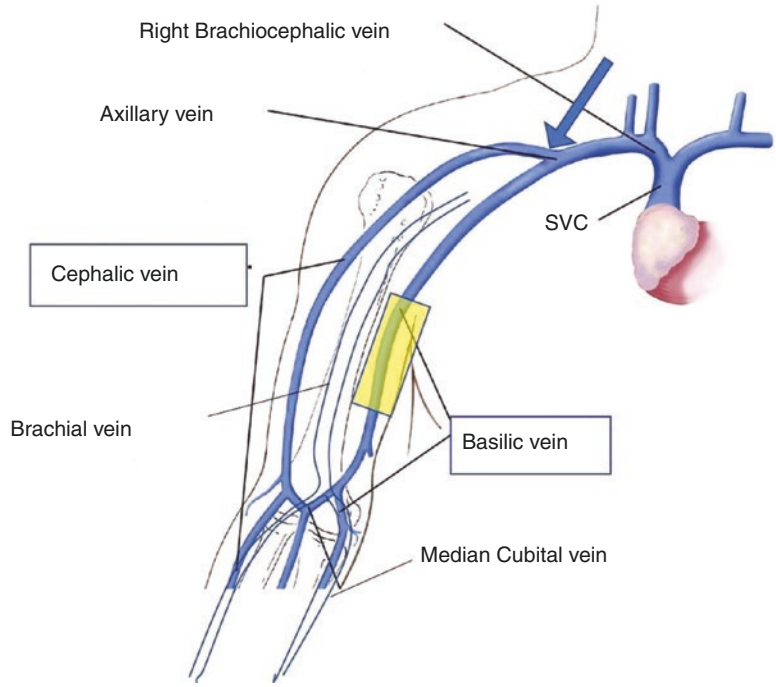

Fig. 1 Upper limb veins. Yellow box denotes the ideal site for peripherally inserted central catheter (PICC) insertion. Arrow depicts the acute turn of cephalic vein at its confluence with the axillary vein

risk of infection whereas too distal a location limits movement at the elbow. The acute turn of cephalic vein at its junction with the axillary vein (cephalic arch) may result in negotiating the catheter centrally, especially when the procedure is performed at the bedside. The brachial vein is better suited than cephalic vein; however, its close proximity to the median nerve and brachial artery relates to a slightly higher rate of complications.

Local analgesia with 1% lidocaine is sufficient in most cases. Under sonographic visualization, a micropuncture needle is advanced into the vein of interest. The vein is compressed with the needle tip and tented. A minimal forward impulse is given to the needle to pop through the proximal venous wall (Fig. 2). A single-wall puncture is preferred. Once dark venous blood is observed dribbling from the needle hub, a microwire is carefully advanced through the needle. The advancement of the wire should be observed under fluoroscopy. A failed puncture often results in a small hematoma obscuring the vein. Spasm and thrombosis may occur as well. A more central location along the vein is selected for further attempts. A venogram to evaluate for central occlusion or to demonstrate a suitable collateral vessel may be performed in the event of multiple unsuccessful attempts.

Using a standard access set, a 6-Fr peel-away sheath is inserted over a 0.018-inch microwire (Fig. 3). The tip of the wire is advanced into the IVC to ascertain venous location and then retracted to the level of the SVC/right atrial junction. The desired length of the catheter is then measured using the measuring guidewire. The guidewire has marks for various lengths. The distance from peel-away sheath hub to skin site (roughly 4 cm) is taken into account. The catheter is then held parallel to the wire and cut to an appropriate length.

The catheter tip is advanced to the SVC/RA junction over the wire (CXR with tip). The guidewire is removed and the sheath is peeled back. The catheter is sutured into position and the hubs are flushed with heparinized saline.

2.3.2 Non-tunnelled Central Catheters

Internal jugular vein is the preferred target for central venous access. Imaging guidance by ultrasound offers greater success in achieving

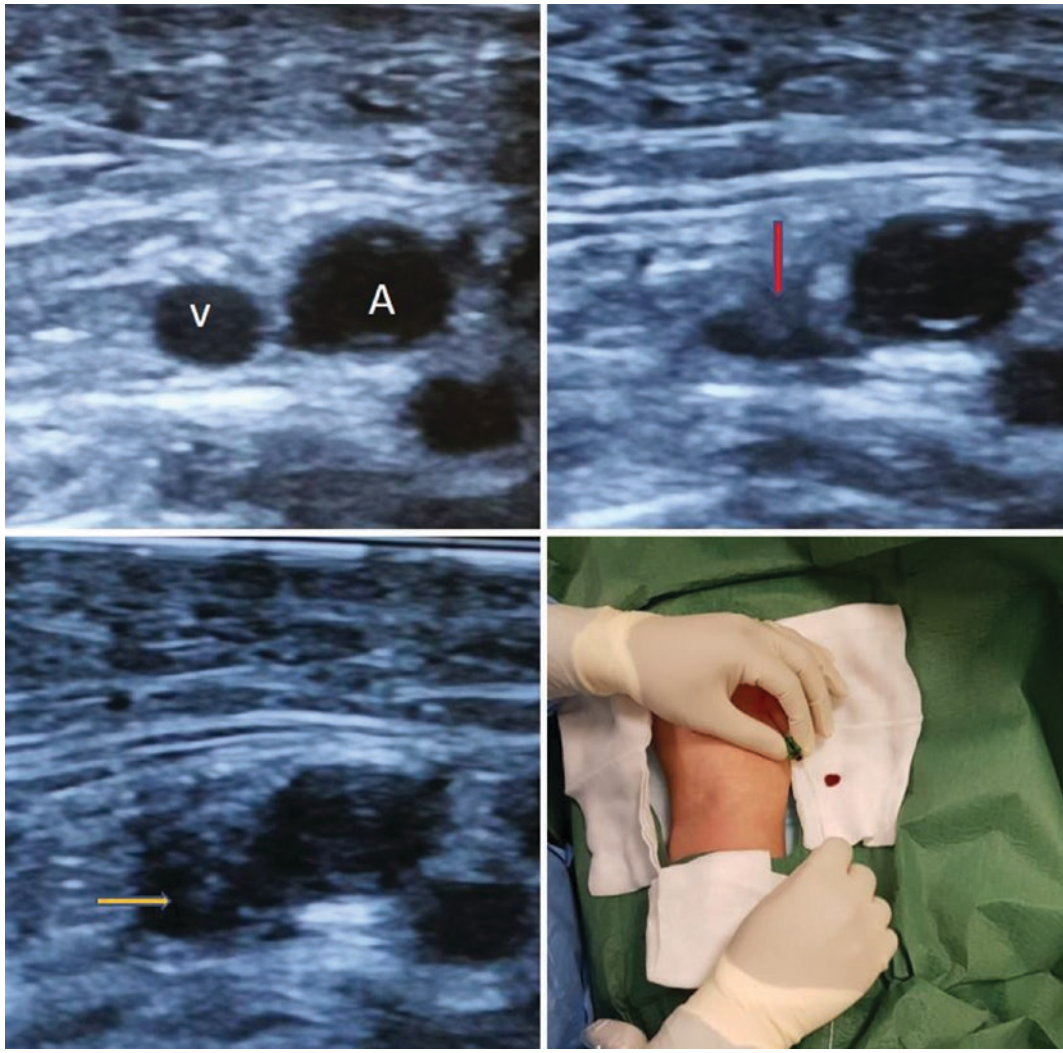

Fig. 2 Access for PICC insertion. Ultrasound guidance helps in avoiding the inadvertent puncture of artery (A). The needle indents (red arrow) the wall of the vein (V) and with a gentle forward impulse it pops into the lumen of the vein (yellow arrow). As the venous blood spontaneously oozes out of the needle hub, a guidewire is gently advanced

access and is safer for patients than blind access based on surface anatomical landmarks. Right-sided access is favored as it offers a direct path to the right atrium (Gordon et al. 1998). The left internal jugular makes a turn at the junction with the left brachiocephalic vein and another turn at the superior vena cava (SVC). Sonographic evaluation before prepping the site should be routinely done to confirm patency of internal jugular vein, determine its relation to common carotid artery and assess for central venous occlusion. An attenuated internal jugular vein with multiple collateral veins in the lower neck suggests central venous occlusion (Chung and Beheshti 2011).

Following standard sterile preparation, a 21-gauge micropuncture needle attached to a slip-tip 5 mL syringe filled with a small amount

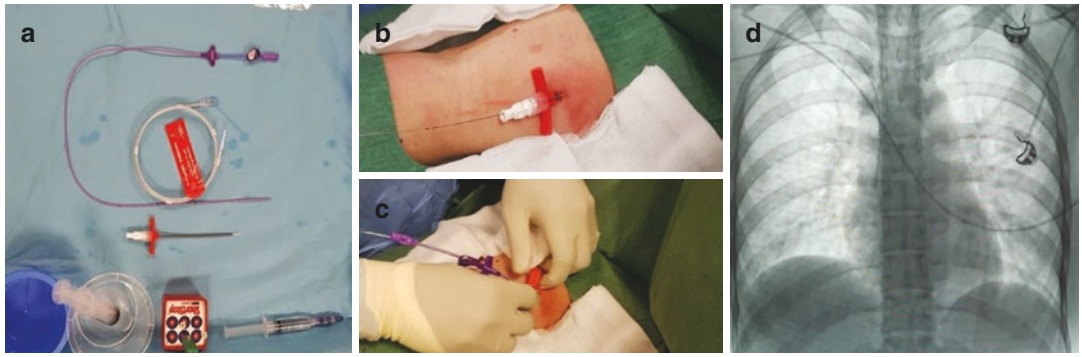

Fig. 3 Components of a standard PICC insertion set (**a**) include the 21 G needle, catheter, guidewire and a peel-away introducer sheath. The 6Fr peel-away sheath is inserted over a guidewire (**b**) and through this the catheter cut to appropriate length is advanced (**c**). Radiograph demonatrates the expected position of the catheter tip at the level of cavoatrial junction (**d**)

of heparinized saline is advanced into the internal jugular vein under direct US visualization. A puncture closer to the clavicle is more comfortable for the patient. Additionally, it facilitates future conversion to tunnelled access if required (Chung and Beheshti 2011). To facilitate puncture lower on the neck, the transducer is placed parallel abutting the clavicle and the access needle is targeted to the lateral wall of the internal jugular vein (Fig. 4). A single wall puncture is performed. Under ultrasound visualization, the needle is advanced through the subcutaneous tissues until it tents the proximal wall of the vein. A steady one-time impulse pops the needle into the lumen and the echogenic tip of needle is confirmed within the lumen of the vein (Fig. 4). In case of accidental common carotid puncture, the access should be abandoned and the site should be gently pressed for 10 min.

A 0.018-inch micropuncture wire is advanced into the needle gently tipping the needle caudally and the wire is observed under fluoroscopy. If significant resistance is met and microwire coils on itself and does not straighten, the wire and needle are withdrawn as a unit and light pressure is held for a few minutes. Pulling the wire through the needle may sheer off the tip of the microwire, especially if its kinked. Once the wire has been advanced into the SVC, a small skin incision is made, cutting along the needle. The needle is removed and the co-axial sheath is advanced. The inner sheath and the microwire are then withdrawn together. A finger is kept over the hole of the outer sheath to minimize bleeding and decrease the risk of air embolus. A 0.035-inch wire of choice, usually a J wire supplied with the kit is advanced into the SVC. The outer sheath of the micropuncture is removed, and sequential dilatation to the size of the catheter is performed. The catheter is then advanced over the wire to the junction of the SVC and the right atrium or the upper right atrium. A very low location in the atrium may induce ectopic beats or the end hole may get opposed against the atrial wall occluding the flow. Too high a position in SVC increases the risk of central venous stenosis.

2.3.3 Femoral Vein

Femoral access is associated with a higher rate of infectious complications, thus it is obtained when the internal jugular vein is not patent or neck access is not possible. The femoral vein lies medial to the femoral artery and should be accessed overlying the femoral head, as this allows compression of the vessels in the event of an unsuccessful puncture. Under ultrasound guidance, the needle is advanced in a similar fashion as described for the internal jugular venous access, aiming cephalad until the proximal wall of the femoral vein is tented. A single

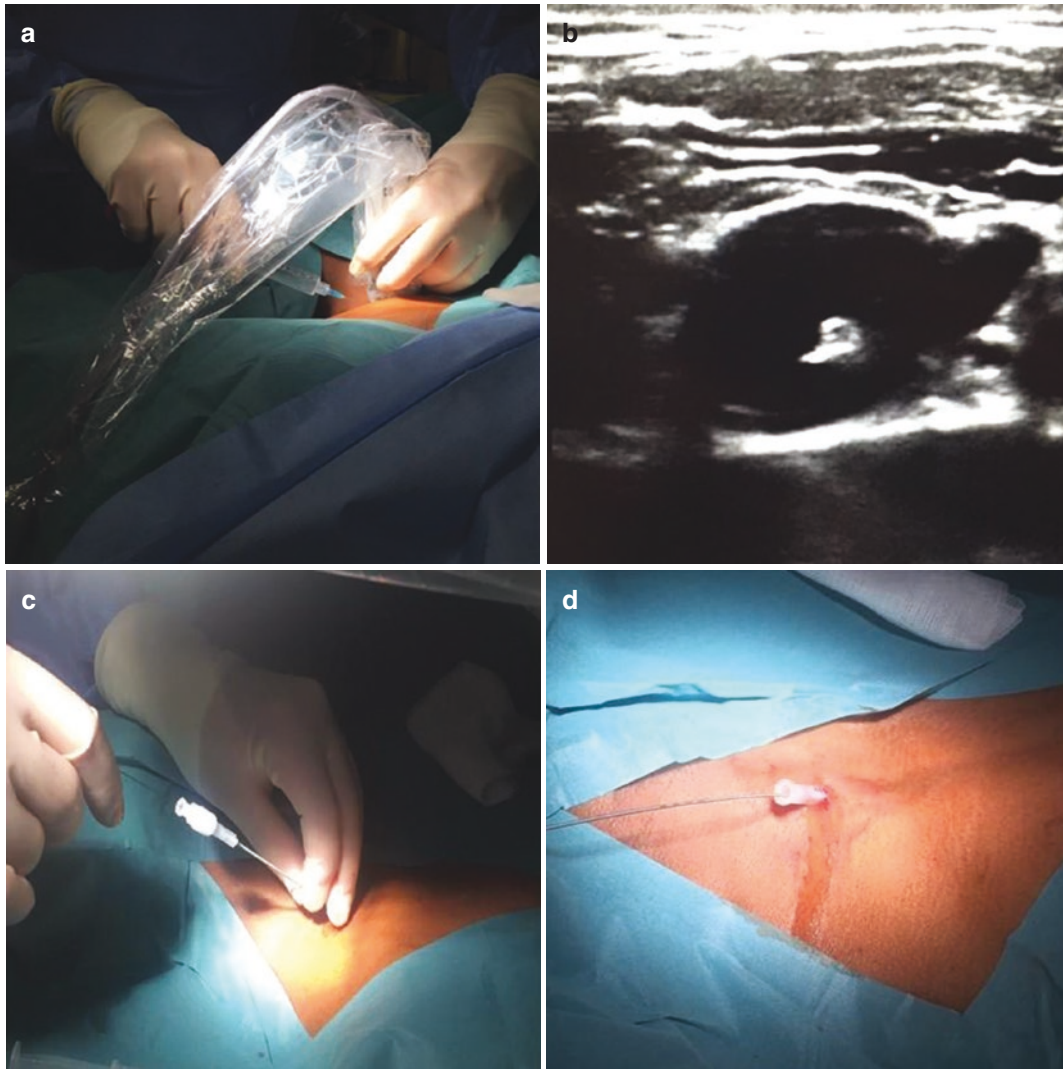

Fig. 4 Right internal jugular venous access using the micropuncture set. The ultrasound probe is held parallel to the clavicle (**a**) and the internal jugular vein is punctured under sonographic visualisation (**b**). The 4F sheath with its dilator are advanced over the 0.018 are remo inch mandril wire (**c**). The dilator and mandril wire are exchanged for a 0.035′ Teflon guidewire (**d**), over which the central venous catheter is inserted

wall puncture is made as described above and the line placement is done in an identical manner.

2.3.4 Subclavian Vein

Subclavian access should generally be avoided unless internal jugular and femoral accesses are not available as it is associated with high rates of thrombosis and higher complications such as pneumothorax (Chung and Beheshti 2011). For subclavian vein accesses, a point near the lateral half of the clavicle is selected. A more central accesses may result in the compression of the catheter between the anterior first rib and clavicle. The ultrasound transducer is oriented perpendicular to the clavicle, which allows visualization of the subclavian vein, artery, and pleura. The subclavian vein is non-pulsatile, superficial to the artery and distends with Valsalva. A left-sided approach is preferred to the right, as the left brachiocephalic vein makes a less acute curve than

the right as it joins the SVC. The procedural steps are identical to those described above.

3 Tunnelled Central Venous Catheters (TCVC)

3.1 Indications

Tunnelled cuffed central venous catheters are large-bore catheters placed through an internal jugular (IJ), subclavian, or femoral venous access. These are primarily used as temporary hemodialysis access in patients with end-stage renal disease. In palliative care, the TCVCs are used when infusion and parenteral nutrition therapy are required for an intermediate duration of 1–6 months. The subcutaneous tunnelling provides stability to the catheter position and helps in reducing the chances of infection. The likelihood of infection is decreased as the skin entry site is distant from the venotomy site. In addition, the polyester cuff attached to the tubing provides a fibrous seal which acts as a mechanical barrier to bacterial colonization (Heberlein 2011). The clinical indications are essentially similar to those described for non-tunnelled venous access.

3.2 Contraindications

TCVCs insertion is contraindicated in the settings of impaired coagulation or active infection. An international normalized ratio (INR) of <1.5 and platelet count of >50,000/μL are desired. However, the procedure can be safely performed with INR values up to 2 (Haas et al. 2010), depending upon the clinical necessity. Since, the cuffed tunnelled catheter is a kind of implanted device, its placement in patients with active infection should be deferred until blood cultures are negative.

3.3 Patient Preparation

Any available imaging that includes the proposed access site should be reviewed to look for a disease process that may obstruct access or result in the catheter traversing a radiotherapy field. Prophylactic antibiotics prior to the placement of a tunnelled central venous catheter does not seem to have a significant beneficial effect on catheter-related infections (Van de Wetering and van Woensel 2007). The use of prophylactic antibiotics hence should be carefully evaluated as overzealous administration carries the risk of emergence of multidrug resistance strains. The patient needs to be nil by mouth for 4–6 h in preparation for moderate sedation. Prior imaging and interventional studies should be carefully evaluated to choose the most suitable access site.

3.4 Technique

The standard access site for TCVCs is right internal jugular vein with subcutaneous tunnel created in the right pectoral region. The access site should be thoroughly cleansed and prepared. Iodine-based antimicrobial solutions in addition to the standard preparations are often used. The procedural steps of securing access into a central vein are similar to those described above. The only difference being creation of a generous opening at the internal jugular or femoral venous access site with a bigger incision and blunt dissection. This facilitates the subcutaneous canalization through the same incision and avoids kinking of the catheter at the turning point.

The central venous access is secured with a 0.035″ guidewire in the IVC. A micropuncture set may be used for initial access. The site for tunnelling is generously anesthetized with local anesthetic. A stab incision is created with the scalpel, just wide enough to seal the cuff of the catheter. Blunt dissection may be carried with a forceps or surgical clamp. The catheter is loaded onto a tunneller, passed through the subcutaneous tract and cuff positioned in the middle of the tract (Fig. 5). The length of the catheter can be estimated by externally placing the catheter attached to tunneller over the patient's thorax and checking with fluoroscopy. Otherwise, it can be measured using the mandril wire used for initial access.

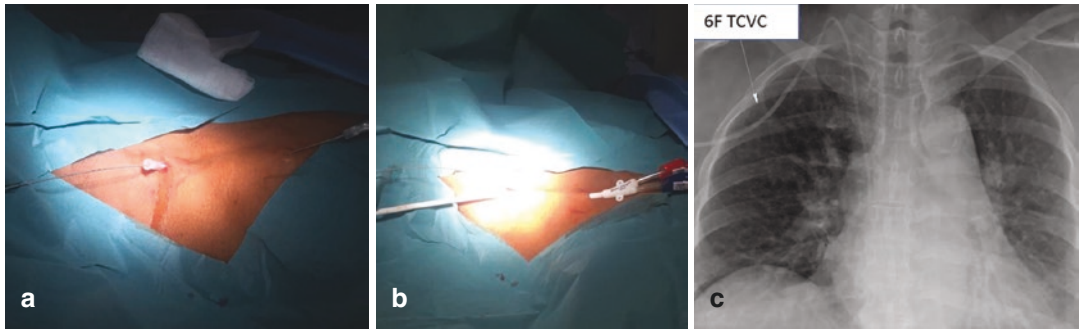

Fig. 5 Photographs taken during the insertion of tunnelled central venous catheter demonstrate creation of subcutaneous plane (**a**) using the diluted local anaesthetic agent followed by tunnelling of the catheter through the plane (**b**). Chest radiograph (**c**) shows the expected course of the catheter with its tip at the superior vena cava/right atrium junction

A peel-away sheath is advanced over the guidewire. Sequential dilatation with appropriate dilators may be required to accommodate the peel-away sheath. The wire along with the inner dilator of the peel-away sheath is removed. Most of these sheaths have valve to prevent air embolism. If not, the lumen must be tightly covered with finger or a clamp. Asking the patient to hum or perform a Valsalva reduces chances of air aspiration. The tip of catheter is advanced through the peel-away sheath as far as possible and the sheath is split. The tunnelled catheter is adjusted to smoothen the course of the catheter into the IJV and position its tip at the superior cavo-atrial junction.

4 Subcutaneous Ports

4.1 Indications

The totally implanted venous access device (TIVAD) or subcutaneous port consists of a reservoir connected to a central venous catheter. The extra-venous portion of the catheter and the attached reservoir are completely imbedded in the subcutaneous tissue. As such, the ports have the lowest rates of catheter-related bloodstream infections amongst all the central venous access devices (Maki et al. 2006). The ports require minimal home care and are less prone to environmental contamination, however, are more expensive to insert and remove.

The subcutaneous ports are best suited for long-term intermittent chemotherapy (Walser 2012). Although not the first choice for chronic continuous intravenous access, the ports may be used for hydration, continuous intravenous (IV) medications (antibiotics), blood transfusions, or parenteral nutrition (Gonda and Li 2011).

4.2 Contraindications

Similar to tunnelled catheters, contraindications to the insertion of subcutaneous ports include active infection and uncorrectable coagulopathy. The patients with active infection or bacteremia should be treated appropriately until the underlying process has resolved. Patients with a coagulopathy or those taking anticoagulants should ideally be corrected until the international normalized ratio (INR) is 1.5 or less and the platelets are more than 50×10^9/L.

4.3 Technique

Ultrasound-guided internal jugular access is the preferred approach. The IJ access allows better hemostasis in case of inadvertent arterial puncture, reduces risk for pneumothorax, and precludes pinching of the catheter (Gonda and Li 2011).

Meticulous skin preparation and aseptic technique are important to reduce the risk of

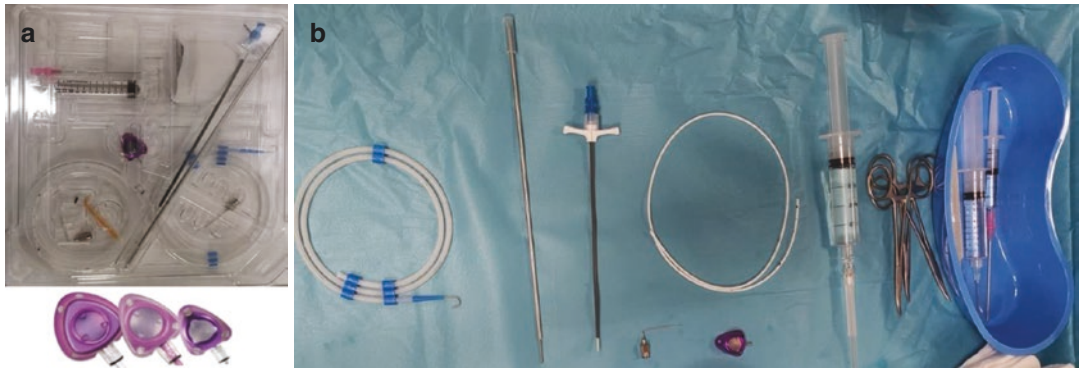

Fig. 6 The subcutaneous ports are typically supplied with the access needle, peel-away sheath, tunneller, guidewire, Heuber needle (for flushing and aspirating the port) and the catheter tubing (**a**). A typical trolley set up for insertion of subcutaneous ports (**b**)

infection. All instruments should be well organized on the procedure table (Fig. 6). The internal jugular access is obtained in a similar fashion to the previously mentioned non tunnelled central catheter insertion. The 0.018″ mandril wire is advanced into the right atrium under fluoroscopic guidance. Clamps are used to mark the wire for the required catheter length.

A suitable port location is determined in the infraclavicular space, and the area is liberally anesthetized with 1% lidocaine. The catheter and the port can be assembled and tested while the lidocaine takes it effect. The junction of the port and catheter is tested by accessing the port with a Huber needle, flushing the catheter, and pinching off the distal end of the catheter to check for leak at the port/catheter junction.

A transverse incision is made, slightly longer than the width of the port and a subcutaneous pocket is created by blunt dissection. The port is placed in the pocket to ensure that it snugly fits into the space. The skin edges are pulled together to make sure that there will not be undue tension on the incision site after closure. Sometimes, if the pocket is too large or the patient is obese, it is prudent to place anchoring sutures to avoid flipping of the port within the pocket.

The tract between the pocket and the access site is anesthetized with 1% lidocaine and the catheter is subcutaneously passed through using a tunnelling device. Once the catheter is brought through the tunnel, the port is positioned within the pocket with or without the anchoring sutures. The tunneller is removed and the catheter is cut to the appropriate length by placing it taut against the clamped 0.018″ mandril wire or estimating using the fluoroscopy. The internal jugular access is secured with an 0.035″ wire and a peel-away sheath is inserted. The catheter is fed through the sheath. Before pulling the peel-away sheath, the appropriate catheter length may be further confirmed fluoroscopically. The catheter length can still be adjusted if longer than ideal. The peel-away sheath is removed while holding the catheter at the skin insertion site with a thumb or forefinger.

The patency of the port is confirmed using the Heuber needle. The pocket incision is closed in two layers, usually with subcutaneous 3-0 Vicryl followed by a 4-0 Vicryl running subcuticular suture (Fig. 7).

In patients with prior surgery (e.g., mastectomy), radiation therapy or burns, alternative pocket locations may be required. A subcutaneous pocket created over the trapezius or a forearm port should be considered.

5 Complications

The central venous access-related complications can be divided into acute and long term. These are summarized in Table 2 (Nayeemuddin et al. 2013). The incidence of

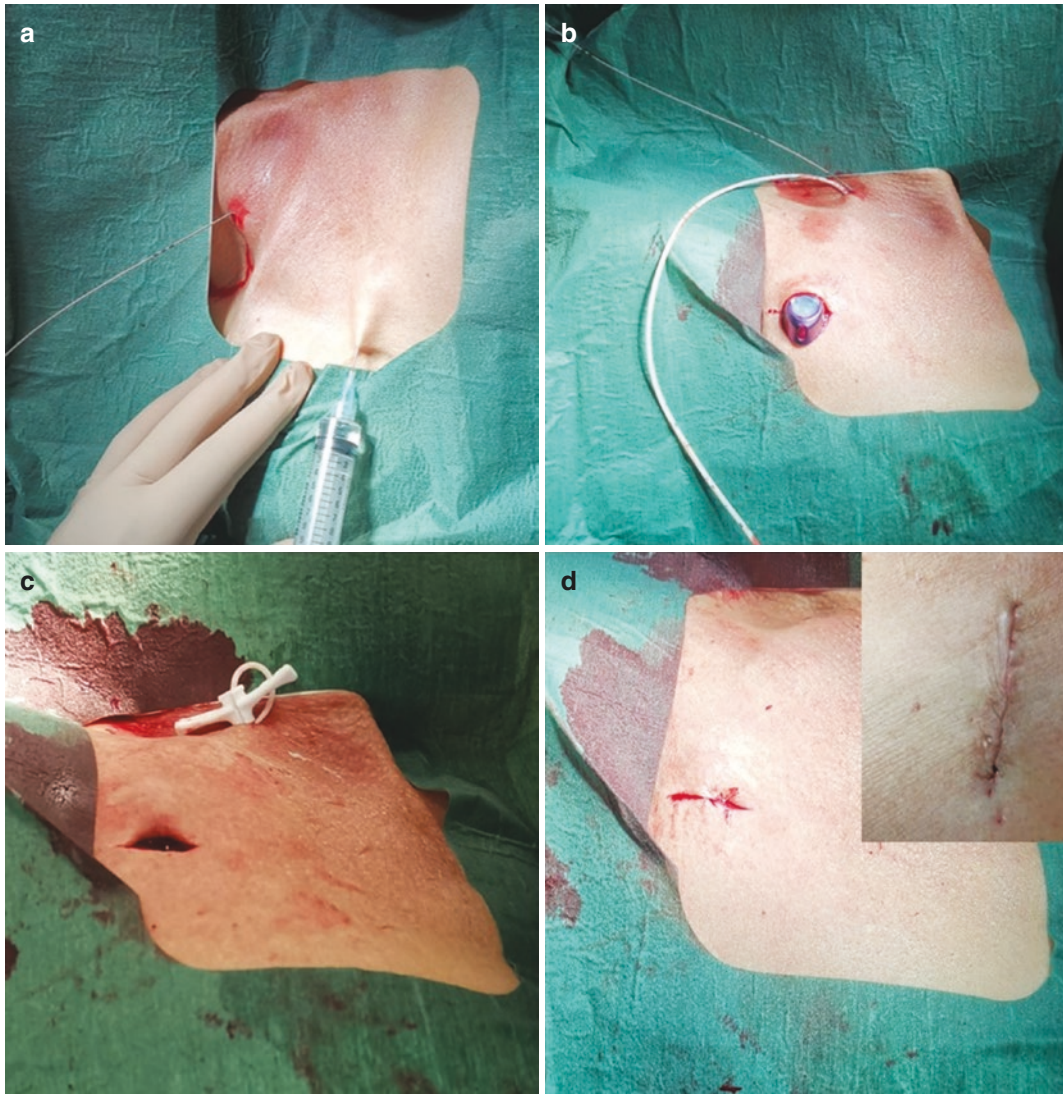

Fig. 7 Subcutaneous port insertion. Following the central venous access, a suitable size subcutaneous pocket is created (**a**). The catheter attached to the port is subcutaneously tunnelled and brought out at the venotomy site (**b**). It is inserted through a peel-away sheath (**c**). The port site is closed in two layers (deep subcutaneous and subcuticular) using absorbable sutures (**d**)

major complications from image-guided central venous access procedures should not exceed 3% (Lewis et al. 1997).

Diagnosing CVC-related infections is not often straightforward. Paired blood cultures (aerobic and anaerobic) from a peripheral vein and the central catheter should be obtained. Catheter sparing diagnostic methods, such as differential time to positivity (DTTP) are reliable but cumbersome to adopt in clinical workflows. Positive culture from the central catheter before the peripheral sample (diagnostic cut-off: 2 h), i.e., DTTP can help to make the diagnosis of catheter-related infection.

Besides, the complications related to the central venous access, the subcutaneous port placement may result in specific complications which are summarized in Table 3 (Walser 2012).

Table 2 Complications related to central venous access

Complications	When to suspect	How to manage
Acute		
Arterial puncture	– Bright arterial blood spurting at the puncture needle – Abnormal course of the guide wire	– Keep the line until a plan of management is made – Compression/endovascular/surgical management
Pneumothorax	Sudden onset of dyspnea, chest pain and desaturation	Insert needle/chest tube to drain the air
Air embolism	– Direct fluoroscopic visualization – Audible drawing of air through the sheath – Desaturation	– If symptomatic, position in Trendelenburg with right side up – 100% O_2, aspiration through the sheath
Arrhythmia	ECG changes and pulse rate variation especially when the guidewire is at right atrium	– Usually transient and asymptomatic – Persistent cases: drugs, electrical intervention and removal/repositioning of the catheter
Bleeding/ hematoma	– Clinically visible/enlarging swelling – Related mass effect symptoms	– Gentle compression is usually enough – Large/expanding: aspiration/drainage
Nerve palsy	Symptoms of neuropraxia of brachial plexus, sympathetic chain or recurrent laryngeal nerve	Usually conservative Recovery may take up to 12 months
Long term		
Fibrin sheath	CVC can be flushed but cannot aspirate	Thrombolytic infusion, fibrin stripping, balloon angioplasty, catheter exchange or line replacement
Central venous stenosis and thrombosis	– Stenosis could be asymptomatic and found on imaging – Isolated facial and extremity swelling – Thrombosis may present with symptoms of pulmonary embolism	– Stenosis or occlusion: angioplasty or stenting – Consider anticoagulation for symptomatic thrombosis – Small/partial thrombus: attempt to break by a J-tip guidewire
Infection	Infection could be limited to exit site, subcutaneous tunnel or bacteremia	Localized to the exit site:—antibiotics alone Infection extending to subcutaneous tunnel or chamber: catheter removal Bacteremia (Blood stream infection): • Empiric antibiotic cover based on local susceptibility data • Antimicrobial lock therapy combined with systemic antibiotics should be tried to salvage the port • Removal of catheter and long-term antibiotics if complicated by hemodynamic instability, osteomyelitis, endocarditis etc. or *S. aureus/Candia* • New catheter 1 week after the patient has remained afebrile with negative blood cultures
Forward migration	Unduly long catheter	Catheter shortening (incision at venous access site, pull out catheter loop and shorten)
Kinks, loops and malposition	Poor function/radiologically identified	– Kinks and loops can be straightened using a super-stiff guide wire – Malposition: forceful saline injection, or snare from femoral approach and pull to satisfactory position
Catheter fracture	– "Pinch-off" sign on a chest radiograph – Can present with sepsis, endocarditis, cardiac perforation, and atrial or ventricular arrhythmias	Percutaneous retrieval using a snare
Catheter entrapment	– Difficult to remove CVC – Due to overgrowth of endothelium into the catheter	– Conservatively managed, though some cases may require surgical venotomy for removal – Prophylactic exchange every 16–18 months

Table 3 Complications specific to subcutaneous port placement

Complication	Comments
Acute	
Chest wall and entry site ecchymoses Adhesive dermatitis	– Reassurance and conservative treatment – May need analgesics – Hypoallergenic dressing
Pocket hematoma	– Clinically significant as it may cause difficulty in port access and wound healing – Increases the risk of abscess – Larger hematoma needs incision and evacuation with resuturing
Flipped port	– May result in inability to access and retraction of the port catheter – Keeping the pocket size just enough in size to accommodate the port and perform anchoring sutures
Long term	
Pocket/tunnel cellulitis or frank abscess or port exposed to skin ulcers	– Need removal/exchange

6 Post-procedure Care

The procedural documentation should include the date of insertion, reason for insertion, insertion site, catheter size, catheter length, excess catheter length outside the patient, number of lumina, and catheter tip position. Catheter dressing and care should be done in strict accordance with the hospital protocols and manufacturers' guidelines. Typically, each lumen of a catheter is flushed with 2–5 mL of heparinized saline (10–100 IU/mL heparin) immediately after placement and after each intravenous infusion.

Meticulous sterile technique when accessing the tunnelled catheters and ports is essential to prevent catheter-related bloodstream infection. Patients should be instructed in proper bathing techniques and avoid completely immersing in the water. The site sutures should be removed by a medical professional in 14 days after catheter placement, usually done by the infusion team.

After the placement of subcutaneous port, the access site is secured with an occlusive dressing. The patient is instructed to keep the original dressing intact for 2–3 days and do not get the access site wet in that time. After 2–3 days, the initial dressing is removed and the site washed with warm water and soap. The occlusive dressing is reapplied after thoroughly drying it. The importance of protecting the dressing and access needle until the time of infusion is emphasized to the patient.

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Feeding Solutions

Sivasubramanian Srinivasan, Karthiraj Natarajan, and Krishna Mohan Gummala

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Abstract

In palliative care, it is an accepted fact that nutrition cannot prolong the life. However, optimal nutrition can help the patient in many ways such as improving physical strength to fulfil his/her final objectives, improving satisfaction of the patient and his/her family and to avoid starvation. Interventional radiology can play an important role in improving nutrition by few ways such as aiding in enteral nutrition by insertion of difficult feeding tubes, insertion of percutaneous gastrostomy or jejunostomy tubes, by insertion of intravenous lines for parenteral nutrition and improving oral feeding by deployment of oesophageal and gastro-duodenal or duodenal stents in cases with malignant obstruction (Acreman 2009).

S. Srinivasan (✉)
Department of Diagnostic Radiology, Khoo Teck Puat Hospital, Yishun Central, Singapore, Singapore
e-mail: srinivasan.sivasubramanian@ktph.com.sg

K. Natarajan
Department of Critical Care, GKNM Hospital, Coimbatore, India

K. M. Gummala
Department of Radiology, Tan Tock Hospital, Singapore, Singapore

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_6

1 Introduction

Patients under palliative care may not be able to have normal food intake. Hence, assisted nutrition is often necessary. The goal of nutrition in palliative care is to improve physical strength of the patients and to avoid starvation. It also improves satisfaction of the patient and close family members. Interventional radiologists can help in improving enteral nutrition or oral intake or indirectly by placement of central lines which can help in parenteral nutrition.

2 Ethical Issues in Nutrition in Palliative Care

Malnutrition is a known problem in patients under palliative care. Cachexia can worsen the morbidity and hasten the mortality in patients with cancer. Nutritional interventions help to minimise the effects of cachexia which is closely associated with anorexia and the inability to take food normally. Nutritional assessment should be holistic and the healthcare professionals performing the assessment should have adequate training (Fine 2006; Acreman 2009). Optimal nutritional assessment and planning requires a multidisciplinary healthcare team approach with the team comprising of physicians, nurses, dietician, and pharmacists. Financial and administrative issues should also be taken into account. The nutritional plans should aim at improving the QoL, maintaining hydration, controlling unpleasant symptoms such as nausea and vomiting and preserving body weight as much as possible (Acreman 2009; Marín Caro et al. 2007). The nutrition plans should also be modified according to the stage and condition of the patient as the disease progresses and frequent discussion with patient and family (Bazzan et al. 2013).

3 Effects of Nutritional Support

Palliative care aims at reducing the suffering and increases the quality of life in patients with terminal or advanced disease. Palliative care is medical treatment that aims to relieve suffering and improve the quality of life of patients with advanced disease. It encompasses the relief of physical, emotional, and existential suffering, as well as the support for best quality of life for both patient and family caregivers.

Cachexia defined as weight loss, anorexia, weakness, and asthenia causing reduced performance status, fatigue, metabolic alterations, and reduced quality of life. Cachexia is an inflammatory process associated with cytokine excess. Weight loss secondary to cachexia is often refractory to therapeutic intervention. The provision of nutritional support alone does not reverse cachexia (Ersek 2003).

3.1 Pathophysiological Changes

Pathophysiological changes in terminally ill patients (especially with cancer) are due to

1. Anorexia and reduced food intake, which is more common in tumours of head and neck and upper gastro-intestinal tract. It may also be due to anticancer medications and radiation therapy.
2. Metabolic changes—increased metabolic activity and demands of the tumour.
3. Inflammatory and hormonal activities such as increased cytokines, increased monocyte and macrophage activation, tumour necrosis factor (TNF) production, and abnormal eicosanoid production. Newer treatment methods include targeting the specific inflammatory and humoral responses.

3.2 Nutritional Support

Nutritional support should mainly be aimed at improving the nutrition of the patient rather than the tumour. Nutritional modifications in cancer patients include the use of halogenated carbohydrates, increased intake of medium chain triglycerides, omega-3 fatty acids, and pentoses. Inhibitors of gluconeogenesis, such as hydralazine sulphate and increased intake of amino acids

such as arginine, glutamine, and omega-3 fatty acids which may help in boosting the immunity are under research. In palliative care in patients with non-cancerous conditions, nutritional support is needed to prevent calorie deficits, loss of lean body mass and muscle mass, and malnutrition. Enteral nutrition is the choice in these patients, if there is no contraindications (Krzak et al. 2011; Marín Caro et al. 2007).

3.3 Artificial Nutrition

Patients need artificial nutrition if oral intake is less than 60% of the nutritional requirement. The goal of artificial nutrition is to improve the overall well-being and resumption of patients' activities. The recommended daily intake of artificial nutrition is around 20–35 kcal/kg, with balanced proportion of carbohydrates and fat (50:50) and a 0.2–0.35 g nitrogen/kg (around 1.2–2 kg protein/kg/day) and appropriate electrolytes, vitamins, and trace elements. Commercially prepared enteral feeds include polymeric feeds which contain protein as nitrogen source, elemental feeds which contain pure amino acids or predigested protein or disease-specific feeds (Ersek 2003).

4 Interventional Radiology and Nutrition

Interventional radiology can help in improving nutrition in many ways (Table 1).

4.1 Enteral Feeding

Enteral nutrition is used when the digestive tract is intact and functioning well.

There are several advantages of enteral feeding compared to the parenteral feeding which includes, maintaining physiological process of digestion and physiological barrier function of intestinal mucosa.

Enteral nutrition can be achieved by nasogastric tube placement. Although traditionally, the nasogastric tube is placed by blind bed-side technique, fluoro-scopy guided over the technique has many advantages, especially in debilitated patients with impaired swallowing mechanism, in patients with pharyngeal or oesophageal obstruction and in patients with large hiatus hernia. Technical success is also higher with fluoroscopy-guided transnasal nasogastric tube placement (Kim and Shin 2017).

4.1.1 Nasogastric Tube Insertion

The conventional nasogastric tube such as Ryles tube are not designed for over-the-wire insertion. However, in patients with upper airway/pharyngeal or oesophageal malignancies, end-hole tubes such as Kangaroo™ (Covidien, Mansfield, MA, USA) are the choice. The patient is positioned supine on the fluoroscopy table and lateral projection is ideal to visualise the nasopharynx. The lateral projection also helps in avoiding the trachea. Usually, in debilitated patients the oesophagus can be entered using an angled angiographic 4Fr or 5Fr catheter and hydrophilic wire. Feeding tubes without end hole can be placed over a wire with or without creation of end hole. Studies have proven that fluoroscopic guidance for NGT insertion is safe and effective in difficult cases such as advanced head and neck neoplasms (Chen et al. 2019; Acreman 2009) (Fig. 1).

4.1.2 Nasojejunal Tube Insertion

Nasojejunal tube is indicated in patients who have high risk of aspiration, patients with

Table 1 Role of IR in improving nutrition

Enteral nutrition	Improving oral feeding	Parenteral nutrition and Parenteral nutrition and hydration
• Difficult nasogastric, nasojejunal and nasogastrojejunal tube insertion • Gastrostomy, Gastrojejunostomy and percutaneous jejunostomy insertions	• Palliative stent insertion in inoperable oesophageal and gastric outlet malignancies	• Insertion of suitable peripherally inserted central lines or central lines

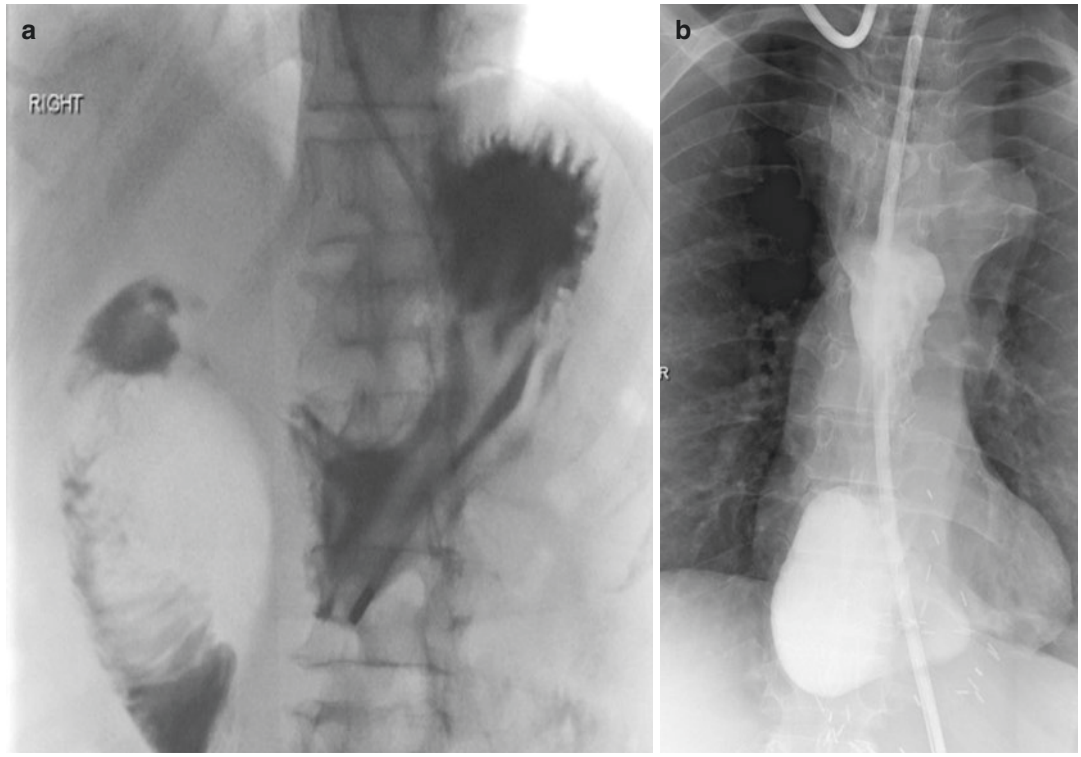

Fig. 1 (**a**) Radiologically inserted nasogastric tube in a technically challenging patient. (**b**) Feeding tube inserted in a patient with recurrent neoplastic strictures after oesophago-gastrectomy. Two lumen gastrojejunal tube was successfully inserted after initial catheterization with hydrophilic wire and angiographic catheter (4French size)

gastroparesis or atony, patients with pancreatitis and patients who have gastro-duodenal obstruction. Insertion of tube beyond the pylorus can be difficult and sometimes need angiographic catheters and wires for initial placement (Pearce and Duncan 2002). Nasogastrojejunal tubes are dual lumen tubes with one of the lumens in the stomach (aiding aspiration of stomach contents) and the other in the jenunum (for feeding) (Fig. 2).

4.2 Modifications of Feeding Tubes

Tubes or catheters can also be directly inserted such as percutaneous gastrostomy or jejunostomy tubes.

4.2.1 Percutaneous Radiological Gastrostomy (PRG)

Gastrostomy provides direct access to stomach for long-term feeding in patients with inadequate oral intake. It can be performed surgically, endoscopically, or radiologically. Surgically placed gastrostomy is outdated and is superseded by endoscopic and radiological insertion. Percutaneous endoscopic gastrostomy (PEG) is the most commonly performed gastrostomy insertion. However, PEG is difficult in patients with pharyngeal or oesophageal obstructions (especially tumours) or where endoscopy is difficult. In those patients, percutaneous radiologic gastrostomy (PRG) is indicated (Haber et al. 2017; Szymski et al. 1997; O'Dowd et al. 2004; Given et al. 2004).

Relative contraindications of gastrostomy include colonic interposition of colon, previous gastric surgeries, presence of ascites, coagulopathy, and portal hypertension with varices.

Preliminary steps of insertion include overnight fasting, pre-procedural antibiotics (usually a broad spectrum antibiotic), placement of nasogastric tube. Injection of barium into the stomach through the nasogastric tube is optional. This helps in identifying the stomach and to

differentiate from the colon loops. Before insertion of gastrostomy, preliminary ultrasound may be performed to rule out hypertrophied left lobe and also to mark the spleen. Ultrasound also helps in identifying the rectus abdominis muscles. The procedure is performed under conscious sedation with Midazolam hydrochloride and fentanyl citrate. Continuous monitoring of the vital parameters should be performed as with any interventional procedure.

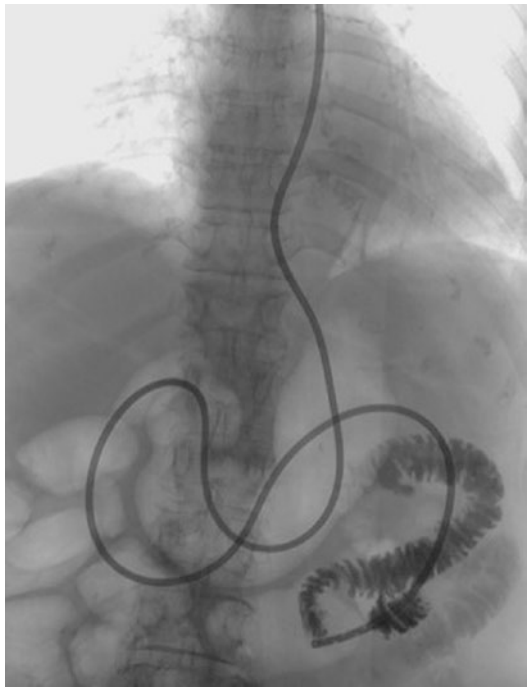

Fig. 2 Nasojejunal tube (If it is dual lumen tube, the shorter lumen is in the stomach which helps in aspiration of the stomach contents)

4.2.1.1 Pull Type

These are the same types used for endoscopic gastrostomy placement. However, they are larger calibre and stable in position. Serial dilatation is not required unlike the push type gastrostomy and peristomal leakage is less with pull type gastrostomy. Wound infection rates are higher in pull type tubes because of contamination from oral cavity and oropharynx.

4.2.1.2 Push Type

Push type tubes are inserted under fluoroscopy after distension of the stomach (through the nasogastric tube). It is secured by inflating the balloon with adequate volume of sterile water (Fig. 3). Although it is technically easier than the pull type gastrostomy, one disadvantage of push type gastrostomy is low retention rate (compared to mushroom type pull gastrotomy tube).

4.2.1.3 Results and Complications

Technical success of PRG is around 95–100%. Thirty-day mortality is around 10.5% (Lim et al. 2016). The mortality is mainly due to existing comobidities rather than directly due to the procedure.

Major complications of gastrostomy insertion less than 6% (Covarrubias et al. 2013), and it includes peritonitis, bleeding, perigastric leak, deep stomal infection, aspiration, and

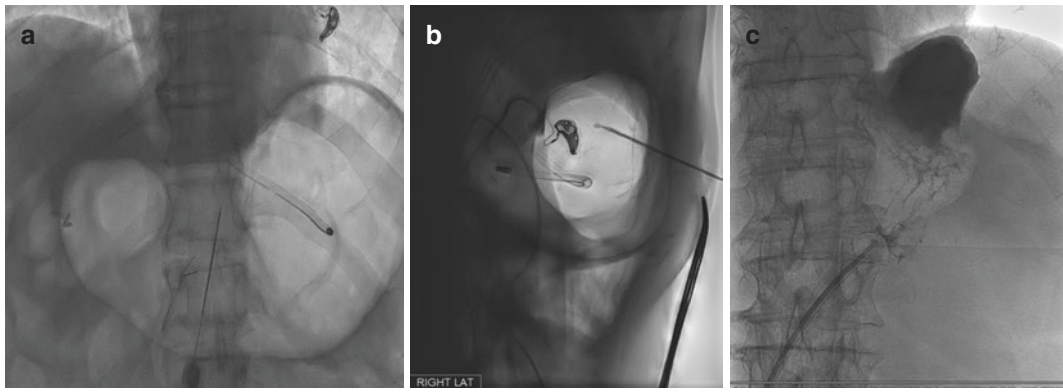

Fig. 3 Push type percutaneous gastrostomy tube. (**a**, **b**) Air-distended stomach (AP and lateral projections). (**c**) Post-insertion of push type gastrostomy tube

displacement of tube. Minor complications include superficial infection, peritubal leaks, or dislodgement. The most serious complication is peritonitis due to intraperitoneal leakage or gastric perforation/tube migration. Erect abdominal radiograph usually demonstrates pneumoperitoneum in such cases and urgent surgical consult is mandatory. Bleeding is very rare especially from the superficial epigastric or gastroepiploic arterial injuries. Aspiration pneumonitis occurs when there is gastro-oesophageal reflux. In such patients, jejunal extension should be considered.

Minor complications include tube dislodgement, peritubal leakage, and superficial infection. Technical success is high with PRG although few studies show increased incidence of complications with PRG (Wollman et al. 1995; Strijbos et al. 2019). The decision for PEG or PRG depends on the indication, suitability, and operator's experience and expertise.

Percutaneous radiologic gastrojejunostomy (PRGJ) is a procedure involving placing of tube into the proximal jejunum through the gastrostomy tube, under fluoroscopic guidance. This technique is called conversion PRGJ (Fig. 4). The conversion is usually done after 2–3 weeks of primary gastrostomy. Gastrojejunostomy has an advantage of reducing the incidence of aspiration compared to gastrostomy tubes. However, since the GJ tubes are longer and narrower, they are prone for blockages or recoil in the stomach.

Fig. 4 Percutaneous gastrojejunostomy. The tip is in the proximal jejunum. The catheter is secured by inflating the balloon with sterile water and it is opposed to the abdominal wall

4.2.2 Primary Radiological Jejunostomy

PRJ is indicated in patients who require a long-term enteral feeding and when gastrostomy is not possible. Direct jejunal access is challenging compared to the stomach. Usually, a 12Fr pigtail-retained gastrostomy tube is used. At some centres, percutaneous jejunostomy is inserted by surgery and subsequent revisions or exchanges are done in the IR suite by interventional radiologists.

4.3 Aiding Oral Feeds by Radiological Stent Placement

4.3.1 Oesophageal Stent

Stenting in oesophageal malignancies is done in patients with inoperable disease. Feeding can be done with gastrostomy. An alternative to that is deployment of stent within the oesophagus, especially when there is a single short segment stricture in mid or lower oesophagus. The goals of palliative management in such patients is to relieve dysphagia, to maintain nutritional status of the patient, and to exclude any oesophago-tracheal or bronchial fistulas (Lowe and Sheridan 2004). The stents are usually made up of silicone or polyurethane. The technique involves slow serial predilatation and deployment of stent. Stenting of oesophagus in such patients is done under fluoroscopy with moderate sedation. Stents can be covered or partially covered or uncovered stents (Fig. 5). Covered stents are very useful in exclusion of oesophago-tracheal fistula; however, they have the risk of migration.

4.3.2 Gastro-duodenal Stent

Palliative gastro-duodenal stent is useful in patients with inoperable gastro-duodenal obstruction. The stent has proven benefit with quick resumption of oral intake and reduced inpatient hospital stay (Upchurch et al. 2018). The stent can be deployed by trans-oral approach with initial access with angiographic 4Fr or 5Fr catheter access with hydrophilic (0.035″ wire). The

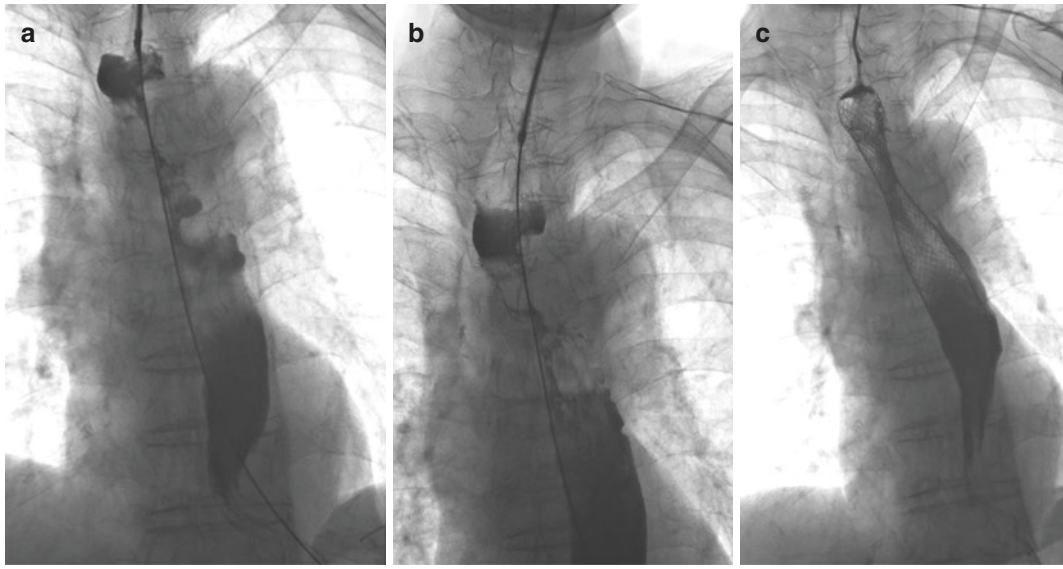

Fig. 5 (**a**) Trans-oral Oesophageal stent insertion. (**a**, **b**) Oesophagogram showing narrowing in the upper and mid thoracic oesophagus due to locally advanced neoplasm. (**c**) Successful deployment of a partly covered stent (23 mm)

catheter is exchanged for a long 10Fr sheath and stent is deployed usually without predilatation (Fig. 6). Transgastric approach can be used if the obstruction cannot be crossed by transoral route. It is done through a gastrostomy access after placing gastropexy sutures. A temporary gastrostomy is placed for 2 weeks to allow the tract to mature. Very rarely a transhepatic route may be possible especially in recurrent obstructions of distal afferent loops in Rou-en-Y oesophagojejunostomy.

4.4 Parenteral Nutrition

Parenteral nutrition (PN) in palliative care setting is a matter of debate and healthcare providers need to look into in a holistic way of who need to be given PN. As per ASPEN guidelines, PN should be initiated carefully by selected patients who are expected to survive for next 2–3 months and who cannot have oral or enteral nutrition (Worthington et al. 2017).

Suitability criteria for PN in palliative care includes (Fuhrman and Herrmann 2006):

- Presence of a gastrointestinal condition precluding oral or enteral nutrition
- Performance status sufficient to allow some participation in care
- Clinical and medical stability, Karnofsky score greater than or equal to 50 (for adults), expected survival of at least 2–3 months, (No recommendation for specific cut-off on Lansky scale for paediatric patients)
- Availability of medical support for monitoring and follow-up for nutrition and non-nutrition healthcare issues, including symptom management
- Willingness to adhere to scheduled laboratory monitoring
- Availability of caregivers to assist with infusion procedure
- Realistic expectations regarding benefits, understanding about risks and burdens of PN therapy.

4.4.1 Catheter Types and Recommendations

As per ASPEN recommendations, the vascular access devices (VAD) for PN should be based on evaluation of risks and benefits of the device, clinical factors, and psychosocial considerations. The catheter should be of smallest calibre with fewest number of lumens needed for the patient

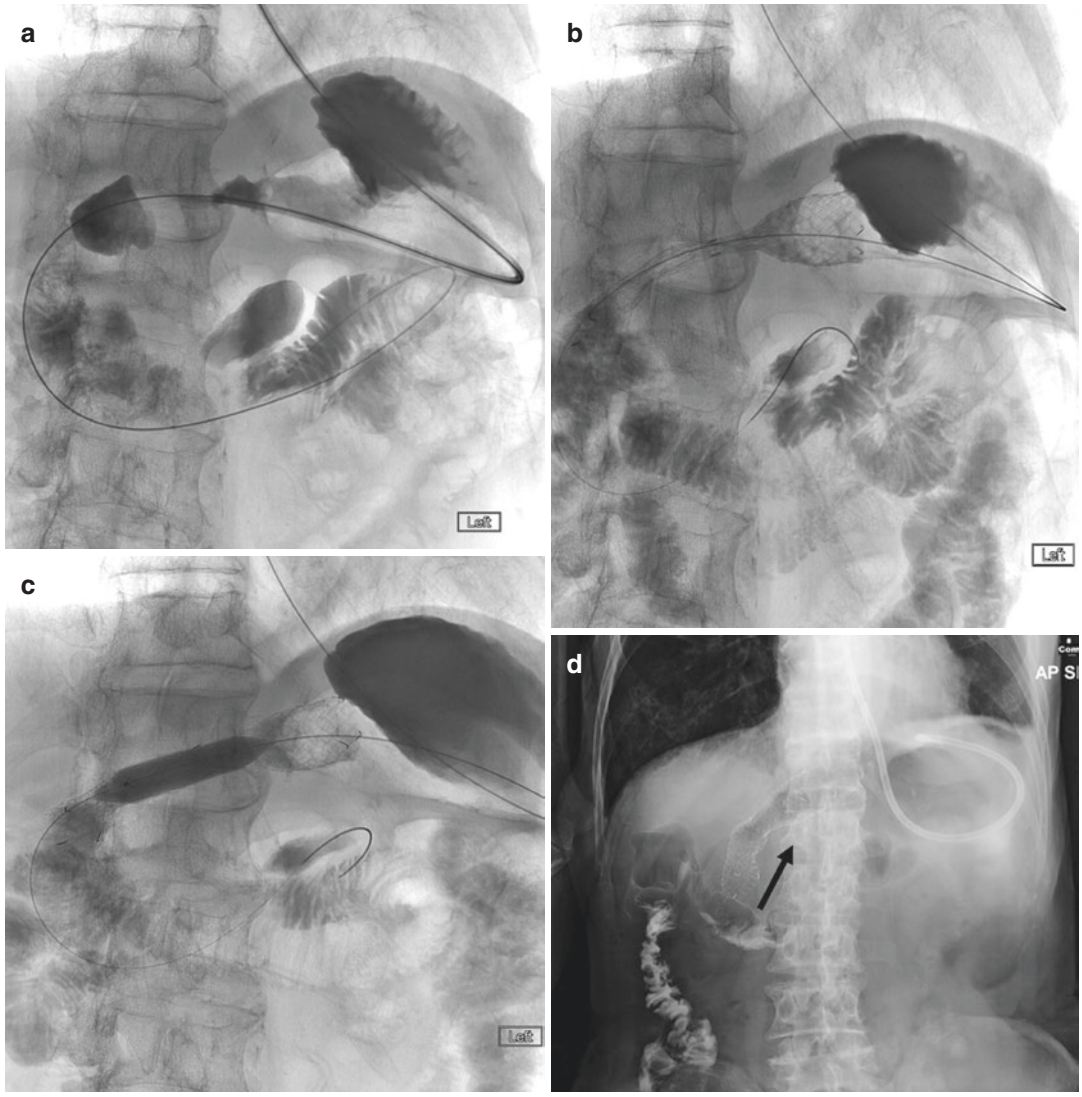

Fig. 6 Trans-oral gastro-duodenal stent insertion. (**a**) Contrast study showing malignant stricture of the distal stomach/proximal duodenum (due to locally advanced carcinoma). (**b**, **c**) Successful deployment of an uncovered (22 mm diameter) stent with post-dilatation with a balloon. (**d**) Post-deployment of the gastro-duodenal stent

and one lumen should be dedicated for PN administration and no other medications or fluid should be administered in the same lumen. The tip of the catheter should be confirmed before administration of the PN (usually at the atrio-caval junction or lower third of superior vena cava for a central line).

The lines that can be considered for administration of PN include peripheral venous catheters, midline catheters, peripherally inserted central catheters (PICC), or central venous catheters (CVC) (Figs. 7 and 8). In the subset of patients with palliative care, PICC or CVC are preferred because of difficulty in peripheral venous access and need for long-term access. The maintenance of PICC is easier and complications are less. The decision need to be individualised by the treating team.

4.4.2 Complications

The complications of PN can be categorised into risks during insertion, delayed complications,

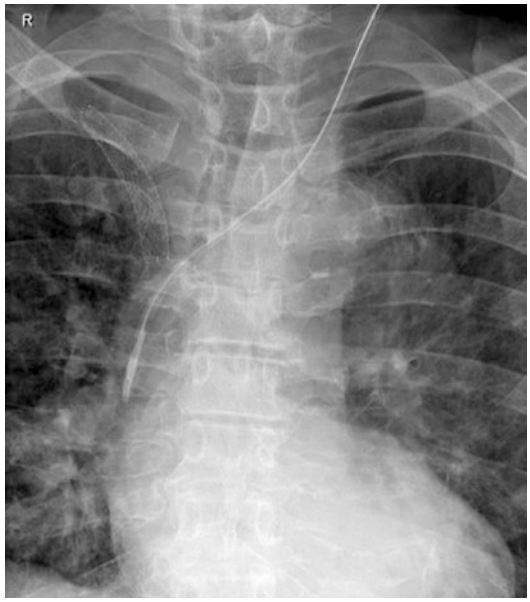

Fig. 7 Central line insertion through internal jugular vein (IJV)

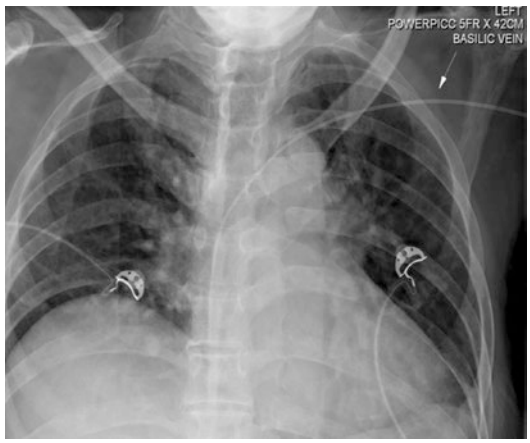

Fig. 8 Peripherally inserted central line inserted through left basilic vein

and metabolic complications (Ukleja and Romano 2007).

1. Risks during insertion include difficult insertion, injury to nearby structures such as arterial puncture, pneumothorax, haemothorax, and malposition of the catheter tip. However, such complications can be minimised or avoided by inserting lines under imaging guidance. Ultrasound guidance should be used for vascular access and radiograph or fluoroscopy to confirm the position of the tip.
2. Delayed complications include air embolus, blockage, infection, catheter-related deep venous thrombosis (DVT), and breakage of catheter.
3. Metabolic complications include hypo/hyperglycaemia, hyperlipidaemia, hypercapnia, acid–base disturbances, electrolyte abnormalities, refeeding syndrome, manganese toxicity, hepatobiliary disorders, and metabolic bone diseases.

4.4.3 Parenteral Hydration

Hydration in palliative care is a topic of debate as there is lack of scientific evidence to prove benefits of assisted hydration. Treating physicians should be aware of the harmful effects of hydration such as pleural effusion, ascites, and peripheral oedema (Good et al. 2014).

5 Conclusion

While selecting the mode of nutritional therapy, the treating team should consider the wishes of the patient under palliation as well as the family members. The nutrition plan should also be reviewed regularly as conditions can change rather quickly in these patients. Although nutritional is an important aspect in palliative care, overnutrition, or over treatment of malnutrition can cause problems, and it can even worsen the patient's quality of life. As the goal in these patients is to improve QoL, a good teamwork is needed and interventional radiology can definitely be a part of the team to help in planning the mode of nutrition.

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Part II

Musculoskeletal Pain Relief Solutions

Imaging-Guided Palliative Procedures: Tendon and Bursa Injection

Anesh Chavda, Alexandra Pender, and Mark Cresswell

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A. Chavda
West Middlesex University Hospital and Chelsea and Westminster Hospital, Chelsea and Westminster NHS Trust, London, UK

A. Pender
Royal Free London NHS Foundation Trust, North Middlesex University Hospital, London, UK

M. Cresswell (✉)
St Paul's Hospital, University of British Columbia, Vancouver, BC, Canada

Abstract

Musculoskeletal pain and inflammation is a common problem in patients post both chemotherapy and radiotherapy and may occur as a direct result of the drugs, radiation, and surgery or may reflect exacerbation of pre-existing tendinopathy and bursitis.

Portenoy et al., 1989 stated that up to 70% of patients with advanced cancer were

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_7

affected by pain. A significant number would however obtain pain control by following the World Health Organization's three-step ladder. Up to 20% would still remain in discomfort, essentially not responding to conventional analgesic regimens (Portenoy, Cancer 63(11 Suppl):2298–307, 1989; Alysa, Curr Opin Support Palliat Care 4(1):11–15, 2010).

This chapter will set out the common causes of drug and radiation-related tendinopathy and bursitis and the most efficacious management techniques. Some may consider this to be the potential fourth step in the WHO treatment ladder (Miguel, Cancer Control 7(2):149–56, 2000).

In addition, we will review the use of systemic steroids and their musculoskeletal side-effects, as well as a treatment for focal inflammation.

1 Introduction

Musculoskeletal pain and inflammation is a common problem in patients post both chemotherapy and radiotherapy and may occur as a direct result of the drugs, radiation, and surgery or may reflect exacerbation of pre-existing tendinopathy and bursitis.

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In addition, we will review the use of systemic steroids and their musculoskeletal side-effects, as well as a treatment for focal inflammation.

2 Image-Guided Tendon and Bursal Injection Basics

Image-guided therapy results in more targeted treatment with less localized side-effects, as the tip of the needle can be directed to the exact location of the abnormality, resulting in the total dose being delivered to the correct location with minimal extravasation to surrounding tissues. The efficacy of image-guided therapy is approximately twice that of blind injections (Portenoy 1989; Alysa 2010). Most superficial soft tissue injections are best performed using ultrasound, as this technique does not require ionising radiation, is well tolerated by patients and allows for a very accurate needle placement. Deeper soft tissue structures can accurately be localized with CT guidance, and if there are adjacent bony landmarks (i.e. joint injections) fluoroscopic guidance is optimal.

For tendons and bursal injections ultrasound is the mainstay for image guidance and will be discussed. All procedures should follow informed consent and utilize sterile technique.

The authors prefer to infiltrate local anaesthetic to the skin and soft tissues overlying the structure of interest and recommend 1% lidocaine without epinephrine. Procedures are performed utilizing a sterile field and aseptic technique as in Fig. 1.

Needle visualization is best achieved by keeping the needle as parallel to the ultrasound probe as possible. If the needle is orientated more perpendicular to the probe (Fig. 2), there is less reflection of the soundwave, resulting in a suboptimal visualization, and the artefact known as

Fig. 1 Interventional setup

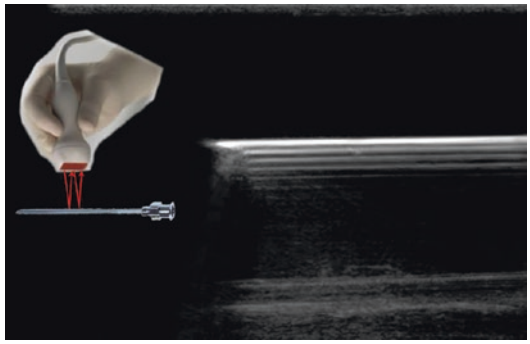

Fig. 2 Needle perpendicular to probe leading to optimal visualization

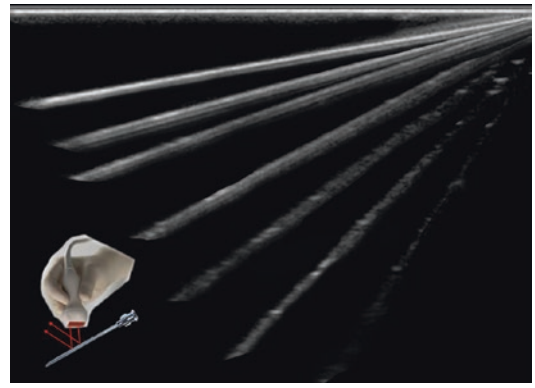

Fig. 3 Anisotropy: As the needle is angled more perpendicular (steeper) relative to the probe, there is less echogenic reflection making it harder to visualize

anisotropy (Fig. 3), which can be a source of frustration for nascent users of ultrasound-guided intervention.

The use of local anaesthetic at the time of any intervention is not only for analgesia, but has a significant diagnostic benefit as well. Post-local anaesthetic injection pain reduction is a useful indicator of whether the imaging finding in question correlates with the patient's perceived pain, and effectively confirms or refutes the clinical impression of the cause of the patient's symptoms. For this reason, all patients are requested to keep a pain diary post-procedure and to present this to their referring clinician.

Tip

Always try and introduce the needle a short distance from the ultrasound probe, as this allows for better visualization of the needle (parallel with the probe) as demonstrated in Fig. 4.

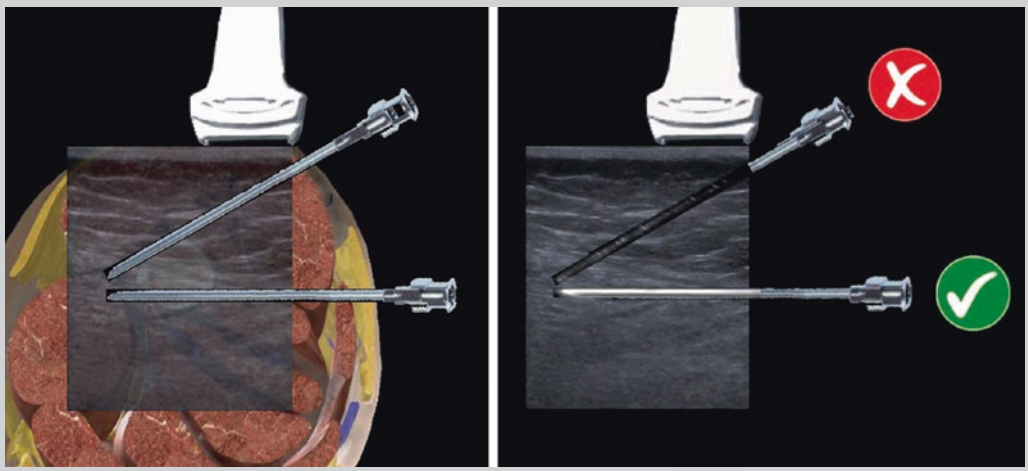

Fig. 4 Needle placement a short distance from the edge of the probe on a rounded structure like a limb, results in the needle being parallel relative to the probe, and this minimizes anisotropy, allowing for optimal needle visualization. Introducing a needle directly adjacent to the probe forces the interventionist to angle the needle markedly to get to the desired target, making the needle difficult to visualize

3 Chemotherapeutic Causes of Arthralgia, Tendinopathy, Synovitis, and Bursitis

Post-chemotherapy arthralgia whilst not common has been documented in the literature on multiple occasions, particularly in relation to treatment of non-Hodgkin's lymphoma as well as lung, breast, and ovarian cancers (Amiri and Rafiei 2010; Lu et al. 2017).

A single case report described the musculoskeletal effects of the immune checkpoint inhibitor nivolumab (Kodama et al. 2017). Following a single infusion for treatment of metastatic lung adenocarcinoma of the lung, the patient developed persistent arthralgia, confined to the knees and shoulders bilaterally, with tenosynovitis and bursitis confirmed sonographically. The patient responded well to a course of oral low-dose corticosteroid (prednisolone). Similar cases were reported by Ngo et al. (2018) and Haikal et al. (2018) respectively, with the development of symmetrical seronegative synovitis resembling a rheumatoid like arthropathy; however, both cases were for the treatment of melanoma. Other immune checkpoint inhibitors recognized to cause arthralgia include atezolizumab, ipilimumab, and pembrolizumab (Naidoo et al. 2017).

There is little direct evidence linking chemotherapeutic agents to tendinopathy and bursitis. More common are these effects following surgery and radiation, particularly in breast cancer patients. These relate to post-surgical pain, radiation fibrosis, and scar tissue which often lead to protective posturing with subsequent shortening of pectoralis muscle and resultant narrowing of the subacromial space. This will eventually lead to a rotator cuff syndrome which encompasses the rotator cuff impingement, tendonitis, bursitis, calcific tendonitis, rotator cuff tears (full or partial thickness), and bicipital tendonitis. If movement is severely restricted, this may precipitate an adhesive capsulitis (frozen shoulder). The aforementioned conditions would certainly benefit from sonographically guided steroid injection, whether related to barbotage, bursal injection, or hydrodistension in the setting of a frozen shoulder, whilst non-steroidal anti-inflammatory medication may also be of benefit (Amiri and Rafiei 2010; Kim et al. 2012).

Hormonal therapies can precipitate musculoskeletal symptoms, particularly aromatase inhibitors (AIs) such as anastrazole. Whilst the precise mechanism of action is not completely understood side-effects of anastrazole can include arthralgia, joint stiffness, bone pain, and an increased risk of osteoporotic fracture (Presant et al. 2007), with a third of patients being severely symptomatic. Carpal tunnel syndrome (Buzdar et al. 2006), tenosynovitis (Morales et al. 2007), and tendinopathy (Martens et al. 2007) are less frequently recorded. The importance of the symptoms has been highlighted in multiple studies where patients discontinued treatment with AIs, reporting joint-related symptoms in up to 60% of participants (Naidoo et al. 2017; Kim et al. 2012; Presant et al. 2007; Dizdar et al. 2009). Morales et al. (2007) demonstrated from a small study of 12 patients that the use of letrozole and exemestane resulted in tenosynovitis of the flexor tendons in the wrist corroborated on MRI. Dizdar et al. (2009) in a larger prospective study was able to show that patients with AI-induced arthralgia had an increased rate of joint effusions and subsequent EMG findings of carpal tunnel syndrome.

Interestingly, not all patients discontinued treatment, indeed many breast cancer patients were able to maintain a level of physical exercise to improve the post-adjuvant chemotherapy experience, with a single study suggesting that patient's perceptions of post-chemotherapy-induced pain (muscle and joint) were not aggravated by training (Andersen et al. 2014).

Management of arthralgia includes paracetamol and non-steroidal anti-inflammatory drugs for mild discomfort. If there is inadequate control of symptoms and limitation of activities of daily living (ADL), then oral steroids such as prednisolone 10–20 mg daily or intra-articular steroid injections for large joints should be considered. If symptoms persist and there is irreversible joint damage, severe pain, or disability limiting self-care and ADLs, then 0.5–1 mg/kg of

prednisolone should be initiated. If there is failure of improvement, referral to rheumatology is advised with consideration of anti-TNF-α therapy (Haanen et al. 2018).

4 Radiotherapy Causes of Myositis, Tendonitis, and Bursitis

Inflammatory changes in muscle can occur due to a multitude of aetiologies. Symmetrical changes are often inflammatory or drug related, whereas asymmetric changes may reflect myonecrosis, radiation, infection, or even compartment syndrome.

Radiation-induced myositis will result in muscular oedema, involving the muscular septae and may induce a localized vasculitis. T2-weighted oedema is evident often with an increase in muscle volume with peak changes demonstrated at roughly 6–12 months following initial treatment. These changes can however persist for several years after cessation of treatment (May et al. 2000). Furthermore, band or stripe-like demarcation of normal and abnormal muscle tissue is a fairly consistent finding in patients who have received radiation therapy leading to a myositis (Mulcahy and Chew 2011). Infarction is a rare complication of irradiated musculature and the presence of liquefaction and irregular enhancement should make one suspicious of the underlying process as these can be responsible for a considerable degree of patient discomfort.

"Radiation recall" is a peculiar phenomenon the radiologist should be cognizant of, as it represents an acute inflammatory response at the site of previous radiation therapy, often induced by a chemotherapeutic agent. The antimetabolite, gemcitabine is quite often the culprit. However, "radiation recall" has also been described following administration of other agents including dactinomycin, anthracyclines (doxorubicin), and taxanes (docetaxel) (Delavan et al. 2015; Ravishankar et al. 2018).

Diagnosis can be confirmed with muscle biopsy. This would require sampling of the most radiologically oedematous component, which is best identified with MRI as areas of hyperintense muscle on fluid-weighted fat-suppressed sequences. Regions of fatty atrophy (T1 hyperintensity) are likely to produce the lowest diagnostic yield, similarly confluent areas of fluid or cystic change hyperintensity may represent necrosis or potentially liquefied haematoma, again yielding little diagnostic value and should be avoided. Ultrasound is the quickest and most efficient modality to gain adequate sample volumes as it is non-ionising and allows for real-time dynamic imaging and sampling. When paired with immediate histopathological review, it results in excellent diagnostic yield. This would allow the radiologist to confirm the adequacy of the sample and would hence obviate the need for further unnecessary intervention. MRI-assisted techniques for muscle biopsy have been described in the literature. Their usefulness relates to the ability of MRI to locate specific areas of residual muscle amongst pronounced areas of atrophy most amenable to biopsy. However, there is a described increased complication rate, most often relating to the proximity of adjacent vasculature on a non-dynamic technique in combination with the vacuum-assisted suction technique (Lassche et al. 2018; Gallo et al. 2018).

5 Systemic Steroid Use in Palliation and Its Effects on Tendons

Steroids exert an anti-inflammatory effect through multiple complex mechanisms based upon an action on nuclear steroid receptors manipulating the inflammatory and immune cascade. By disrupting prostaglandin and leukotriene production, there is a reduction in vascular permeability and therefore build-up of inflammatory cells.

For patients who develop tendinopathy, steroids have served as a viable first choice managing pain and improving mobility. However, over the past decade there has been a gradual reduction in their use for managing tendon disease as

there is a wealth of evidence suggesting their use is more a temporary "fix" with long-term detrimental effects (Topol et al. 2005).

Tendon treatment with steroids is thought to have mixed results. Specifically, a systematic review in 2011 by van Ark et al., reviewed six different treatment types for patellar tendinopathy. These included steroids, platelet-rich plasma (PRP), dry needling, sclerotherapy, autologous blood, aprotinin, and finally high volume injections. It was clear from the results that whilst steroids had benefits in the treatment of acute tendinopathy, the medium to long-term effects were not as positive, with an increased rate of relapse as well as risk of tendon rupture (van Ark et al. 2011).

In oncology, steroids have multiple uses, which are not directly discussed here. In brief their role as anti-emetics is important in chemotherapy regimes, whilst there is evidence for controlling cerebral oedema and treating moderate to severe side effects of immunotherapy (Haanen et al. 2018; Mulvenna et al. 2016; Navari and Aapro 2016) as described above.

Osteopenia is not a common side effect of steroid administration in oncology patients, with most dosing regimens lasting days rather than weeks. Rather, oestrogen deficiency can accelerate bone loss. Oestrogen deprivation occurs in women with breast cancer and men receiving androgen deprivation therapy. Here, rapid bone turnover will lead to a decreased bone mineral density (BMD) and increasing fracture incidence, as high as 50%. Couple this with the immobility associated with oncological treatment and the risk of insufficiency fractures is further exacerbated. BMD could be better assessed with dual energy x-ray (DEXA) scans (Coleman et al. 2013, 2014).

If a prolonged high-dose steroid wean is required to treat severe checkpoint inhibitor side-effects, bone protection should be considered. Bisphosphonates, which reduce osteoclast activity, decreasing resorption and encouraging mineralization, can be used to guard against such complications (Van Poznak et al. 2010; LeBlanc et al. 2009; Hirano et al. 2018; Lancet EBCTCG 2015).

6 Local Steroid Injections to Reduce Focal Inflammation

Guided injection of steroid is commonly used to dampen localized inflammatory change most commonly within bursa and non-weight-bearing tendon sheaths (Bolton et al. 2018; Fawcett et al. 2018). Although effective in diminishing inflammation, steroid does not treat the underlying cause of inflammation and can be associated with tendon tears. It is for this reason that interventionists use steroid injections of tendons and peritendinous soft tissue sparingly (van Ark et al. 2011; Lu et al. 2016).

7 Calcific Tendonitis Intervention

Calcific tendinitis results from hydroxyapatite deposition within the tendon and can be associated with significant pain at rest. The presence of calcification within the tendon however, may not reflect active inflammatory change and one must be cognizant of this to avoid unnecessary intervention. It is useful to directly visualize and sonographically palpate the calcific deposits most likely responsible for discomfort utilising the probe, whilst simultaneously corroborating this as the source of the patient symptoms. If there is doubt, external rotation of the humerus relocates the calcium and repeat palpation in the same dermal location should elicit little if any discomfort, confirming that this is unlikely to be the source of true acute discomfort.

Calcific barbotage requires good analgesia prior to the procedure, as a larger bore (circa 18G) needle is usually required for effective treatment since calcific debris can easily block the needle hub. The intra-tendinous calcified mass is penetrated under sonographic guidance and repetitive pulsation of fluid is performed into the body of the calcific mass, usually utilizing initially local anaesthetic like 0.5% Ropivacaine, followed by a normal saline (Fig. 5). This frequently results in the central calcium within the mass being dissolved by the pulsing fluid and

washed back into the syringe although this is not always consistent. The overlying subacromial-subdeltoid bursa is then finally injected as calcific debris will leak along the needle track created for barbotage and this site of leak will lead to a painful inflammatory response which can be quite disabling. Further calcium is dissolved over time, the remaining marginal calcification can be broken up mechanically by the needle under direct ultrasound visualization. Newer techniques include calcific needling in conjunction with extracorporeal shockwave therapy have shown promise but still require further research (Pakos et al. 2018).

The effectiveness of barbotage procedures in the acute setting has been documented in the literature in multiple studies, through randomized control trials, systematic reviews, and meta-analyses. Of note, is that these studies have primarily been conducted on individuals without significant comorbidities and the benefits of these procedures are questioned in the long term as new data has revealed. In particular, there is emerging evidence to suggest a profound placebo effect. Yet, in the acute setting there is clear evidence that pain relief is pronounced and considering the life expectancy of some patients with advanced malignancy, the usefulness of barbotage in the short term in clear (Lanza et al. 2015; Moosmayer et al. 2017; de Witte et al. 2013, 2017; Yoo et al. 2010; del Cura et al. 2007).

Tip

It is important to keep the syringe lower than the calcium deposit as the calcium fragments become dependent within the syringe (Fig. 5).

Fig. 5 Demonstrating best placement of the syringe during barbotage, which allows for best extraction of calcium

7.1 Rotator Cuff

The rotator cuff represents the most common site of calcific tendinopathy and is frequently associated with significant shoulder pain at rest and with abduction. The presence of hydroxyapatite crystals in close proximity to the bursa, or possibly decompressing into the bursa, can result in intense bursal inflammation in addition to the calcific tendinitis. A relatively painless calcific barbotage procedure can be achieved by thoroughly anaesthetizing the subacromial subdeltoid bursa overlying the rotator cuff prior to commencing barbotage.

Ultrasound-guided calcific barbotage is the mainstay of treatment and has been demonstrated to be effective in a systematic review of 908 patients (Gatt and Charalambous 2014) and in a long-term follow-up study. Post-procedure, patients experienced prompt functional recovery and pain relief of their shoulder symptoms. Treated patients had better outcomes than control patients at 1 year although the difference at 5 and 10 years post-procedure was not significant (Serafini et al. 2009; Aina et al. 2001). Aina et al. described a clinically effective needling techniques and lavage, which they found to be less traumatic than surgery.

Following the calcific barbotage procedure corticosteroid should be instilled into the SASD bursa (Fawcett et al. 2018) to ensure comfort over the short term. Calcific barbotage has been demonstrated to be more effective than SASD bursa steroid injection alone (de Witte et al. 2013). Other techniques include extracorporeal shockwave lithotripsy (ECSWL) although these have not been compared to US-guided barbotage.

7.2 Gluteal Musculature

The greater trochanteric entheses of the gluteus minimus and gluteus medius tendons represents the second most common site of calcific tendinopathy. Rarely calcific tendinitis may affect the femoral enthesis of the gluteus maximus, which can be associated with focal bony erosion (Portenoy 1989; Huang et al. 2017). The patient may present with considerable localized tenderness at the site of the gluteus maximus insertion onto the posterior femoral metaphysis. CT is perhaps the most useful modality with radiography to identify a focus of calcific tendinitis. Comet tail calcification has been described at the site of entheseal insertion, in addition to focal erosion which should not be mistaken for infection (Alysa 2010; Mizutani et al. 1994). Treatments would include physiotherapy, analgesia, and corticosteroid injections. Non-responders may benefit from ultrasound-guided percutaneous needle aspiration and lavage, whilst newer therapies may include extracorporeal shockwave therapy (Pakos et al. 2018).

7.3 Longus Colli

Head and neck cancers are capable of dissecting fascial planes and infiltrating any neck compartment including that of the perivertebral space where the longus colli muscle resides. Rather than direct treatment, the value of radiology in this setting would be assisting in tissue diagnosis, primarily through core biopsy or fine needle aspiration in the hands of a technically adept radiologist.

Rarely, however, longus colli calcific tendinitis immediately inferior to the anterior arch of C1 in the non-oncological setting can result in significant prevertebral soft tissue swelling and pain with swallowing. This is often due to calcium hydroxyapatite deposition and should warrant both clinical and radiological assessment for involvement of other joints. A single case also reported calcium hydroxyapatite in the immunocompromised patient (Estimable et al. 2015).This condition is usually managed with oral non-steroidal anti-inflammatories as trans-oral barbotage would be technically difficult and risk a paraphargyngeal abscess (Alamoudi et al. 2017).

More often the presence of infection may complicate the post-radiotherapy patient, in particular an abscess or fluid collection involving the "danger space" located behind the true retropharyngeal space (anterior to the perivertebral space) is of particular concern as it connects the deep

cervical space to the superior mediastinum, potentiating the spread of infection. Fine needle aspiration of the retrophargyngeal space is a potential route for identifying the offending organism helping guide antibiotic treatment. This would warrant aggressive medical management and potential surgical intervention to prevent the development of a mediastinitis (Shawky et al. 2017).

7.4 Less Common Sites of Calcific Tendinopathy

The origins of the adductor longus and rectus femoris tendons are less common sites of calcific tendinopathy as is the adductor brevis. The management using ultrasound-guided calcific barbotage remains the same (Tamangani et al. 2009; Klontzas et al. 2016).

8 Bursal Intervention

The subacromial subdeltoid bursa is the most commonly injected bursa (Fig. 6). Other common sites of inflammation include the bicipitoradial, olecranon, trochanteric, pre/infrapatellar, retrocalcaneal and intermetatarsal bursa. Inflammation of any of these bursae can be mechanical or inflammatory, both respond well to a combination of local anaesthetic and corticosteroid injection.

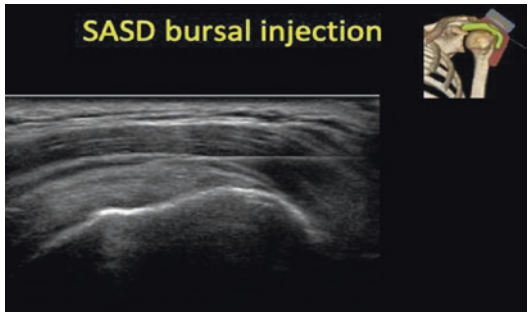

Fig. 6 A lateral approach to the subacromial-subdeltoid bursa (hypoechoic sliver of fluid distends the bursa where the needle is appropriately sited)

Whilst the literature does not describe any specific chemotherapeutic agents affecting any of the aforementioned bursae directly, oncology patients are quite prone to bursitis secondary to immobility and in particular contractures. There is evidence to suggest that imaging-guided bursal injections provide significant symptomatic relief as well as aid in rehabilitation (Fawcett et al. 2018). Furthermore, the development of calcific tendinitis secondary to calcium hydroxyapatite deposition is a particular culprit of patient discomfort and as suggested earlier, calcific barbotage has been demonstrated to have its benefits in acute discomfort and is likely to be of use in allowing rehabilitation (Bolton et al. 2018).

9 Tendon Intervention

Several studies have demonstrated quite consistently the benefits of microtenotomy procedures, commonly augmented with injection of various substances promoting the inflammatory healing cascade. The best substrate for use is slightly contentious and there is often wide variation in local practice dependent on operator experience. In the author's experience, a simple microtenotomy and injection of hypertonic dextrose results in sufficient inflammatory response to achieve excellent results commensurate with the quoted results in the peer-reviewed literature (circa 80% positive results following procedure in terms of pain and ADLs) (Lee et al. 2019). Hypertonic solutions mediate inflammatory responses and tissue healing through inflammatory mediators including endothelial growth factor, platelet-derived growth factor, transforming growth factor beta and connective tissue growth factor. Hyperosmolar glucose will hyperpolarize nerves by opening potassium gated channels and reduce pain fibre action potentials (Hassan et al. 2017).

Whilst a discussion about the wide spectrum of tendon intervention available for tendon injury is beyond the scope of this chapter, we shall focus on more common procedures such as prolotherapy and microtenotomy. There have been a plethora of studies over the last two decades

researching the effectiveness of ultrasound-guided tendon intervention, particularly prolotherapy for tendinopathy. The evidence is still quite mixed. A prospective blinded study in 2007 by Maxwell et al. was one of the earliest to utilize hyperosmolar dextrose in the treatment of chronic Achilles tendinopathy. Through an average of four sessions of 25% dextrose injected at six weekly intervals, they were able to reduce pain scores significantly, with up to 60% pain free at 6 months. Hauser et al. performed a systematic review of dextrose prolotherapy for chronic musculoskeletal pain. This consisted of 14 randomized control trials, one case-control study and 18 case series studies, focusing on lateral epicondylitis of the elbow, rotator cuff injury, and myofascial pain. It concluded that there was low level evidence for the use of prolotherapy in combating tendinopathy (Hauser et al. 2016; Maxwell et al. 2007).

10 Gout and Crystal Arthropathies

Tumour cell lysis in response to systemic therapy can release potassium, phosphorus, and nucleic acids which are metabolized into hypoxanthine and xanthine and then uric acid. Cardiac arrhythmias are common with hyperkalaemia, whilst hyperphosphatemia can precipitate hypocalcaemia (and tetany), seizures, and arrhythmias. Uric acid can induce acute injury through intrarenal crystallization but also through renal vasoconstriction, oxidation, inflammation, and a reduction in renal blood flow (Williams and Killeen 2019).

Crystal arthropathy following tumour lysis is an issue one must be cognizant of in order to avoid a delay in diagnosis. A single case report in 2010 demonstrated the development of acute gouty arthropathy 3 days post-percutaneous radiofrequency thermal ablation. Uric acid and potassium levels were raised, in conjunction with acute knee pain and effusion. Joint aspiration demonstrated monosodium urate monohydrate crystals. Treatment with oral colchicine in this setting was of benefit (Choi and Lee 2010). In the absence of clinically evident tophaceous gout, the role of the radiologist relates to imaging-guided aspiration and microscopy to achieve diagnosis. DECT is an emerging imaging modality used to confirm uric acid deposition without the need for intervention. Chronic changes include juxta-articular erosions with or without soft tissue deposits. The popliteus entheseal insertion is a common site of gouty tophaceous deposition and should always be inspected. Other sites of interest would include the roof of the intercondylar notch, tibial eminence, medial rim of the medial femoral condyle, and lateral rim of the tibial plateau. Tophi themselves can have variable appearances with or without calcified components. On MRI they may demonstrate T1 isointensity and low to intermediate signal on T2 with variable post-contrast enhancement (Igel et al. 2017; Ko et al. 2010).

11 Summary

In the setting of a range of oncological treatments, image-guided therapies for tendinopathy, bursitis, and calcific barbotage are simple cost-effective measures which can provide considerable relief from symptoms and side-effects of treatment and allow patients to tolerate the rigors of therapy and maintain an improved quality of life.

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Cement Consolidation: Vertebral Augmentation and Cementoplasty

Steven Yevich

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Abstract

Structural bone instability from osteoporosis or tumor destruction can result in debilitating pain, fractures, and erosion of muscle attachments. Cementoplasty describes the percutaneous minimally invasive injection of a bone filler to consolidate the weakened bone in order to provide palliative effect and reduce the risk of an impending fracture or progression of an existing fracture. When applied to the spine, the technique is commonly known as vertebral augmentation, a term that encompasses both vertebroplasty and kyphoplasty. Outside of the spine, the procedure is commonly referred to as cementoplasty or osteoplasty, and sometimes with specific anatomical descriptors such as sarcoplasty and acetabuloplasty. This chapter reviews the indications, general techniques, and pitfalls for percutaneous cement stabilization both within and outside of the spine.

Abbreviations

CT	computed tomography
HA	Hydroxyapatite
MRI	magnetic resonance imaging
PMMA	Polymethyl methacrylate

S. Yevich (✉)
Division of Diagnostic Imaging, Department of Interventional Radiology, University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: syevich@mdanderson.org

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_8

1 Introduction

Cementoplasty generally refers to the consolidative technique of cement injection under imaging guidance. Small caliber needles are inserted into a structurally unstable bone that is subsequently reinforced with injection of a bone filler colloquially known as cement. The cement hardens shortly thereafter to restore structural bone integrity and provides resistance to forces experienced during activities of daily living. The immediate goals of treatment are local pain control and preservation of functional activities, which translate to improvements in quality of life, decreased opioid dependence, decreased morbidity associated with immobility, and lower overall healthcare costs (Saad et al. 2007).

This minimally invasive procedure can be performed in the outpatient setting. Durable pain palliation is expected in 1–2 days, once healing from the needle manipulation subsides. The technique can also be applied as a preventative measure for impending pathological fractures (Deschamps and De Baere 2012). In the treatment of malignancy, cementoplasty does not impeded administration of systemic therapies or external radiation treatments. Conversely, cementoplasty may provide the palliative relief to allow a patient to complete a systemic or radiation treatment.

2 Indications

The overarching procedural goal of cementoplasty is consolidation of an osteoporotic or pathologic defect, with fortification along any fracture lines. Appropriate patient selection is fundamental to ensure treatment success. A location of pain must correlate with an osseous defect on imaging. The pain should be mechanical in nature, with exacerbation upon movement or weight-bearing. Sources of pain outside of the bone should be excluded such as neuropathy, arthritis, and bursitis, which would benefit from alternative treatments such as steroid injections.

When considering the location of osseous instability, it is important to consider the force vectors that the unstable bone experiences during the course of daily activities. Cementoplasty is most effective in locations subjected to unidimensional axial forces such as in the vertebral body or acetabulum. Conversely, the procedure is less effective in locations subjected to multidimensional torque stresses, or when the bone destruction involves a joint, muscle origin, or tendon insertion site. Treatment outcomes in long or flat bones that are subjected to substantial torque or flexion stresses might benefit from additional reinforcement by placement of a percutaneous screw or intramedullary rod (Collinge and Crist 2016; Cazzato et al. 2016; Deschamps et al. 2012; Deschamps et al. 2018).

In the case of pathologic disease, tumor characteristics may convey different treatment outcome expectations. For example, while lytic lesions are conducive to cement consolidation, the nonporous nature of sclerotic metastases is often resistant to cementoplasty. Lastly, metastases cause musculoskeletal pain not only by undermining the osseous framework and the integrity of muscle and tendon insertions, but also through factors related to tumor growth such as increased intra-osseous pressure, periosteal stretching, extrinsic pressure on adjacent nerves and muscles, and cytokine-mediated tumor-associated inflammation (Mundy 1997; Figura et al. 2018). A comprehensive treatment should be performed to address all etiologies of pain. For example, if both resting and mechanical pain is present in a patient with a rapidly enlarging and vascular osseous metastasis, then a comprehensive procedure that might provide a more durable treatment effect would a combination of a devascularizing procedure and a locoregional control treatment before cement consolidation (Fig. 1) (Hartung et al. 2016; Wallace et al. 2015; Nakatsuka and Yamakado 2004; Munk et al. 2009).

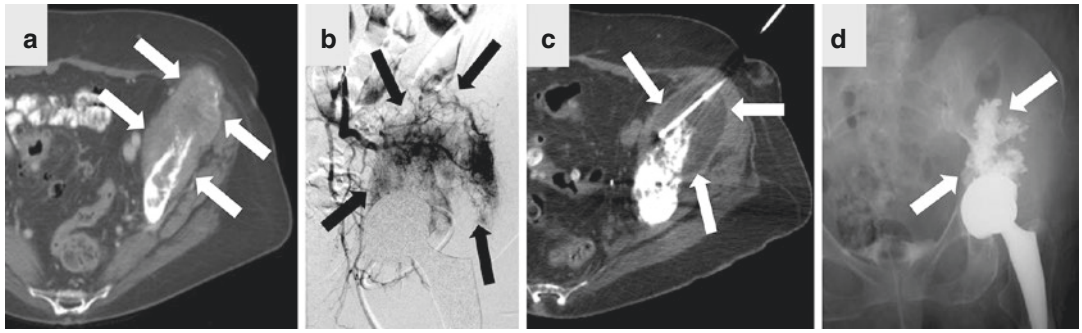

Fig. 1 72 year old woman with a large hypervascular renal cell cancer metastasis to the left iliac bone with involvement of the left superior acetabulum that undermined the existing left hip arthroplasty and results in significant weight-bearing pain (**a**, axial CT with contrast with white arrows outlining vascular osseous metastasis). Comprehensive treatment was performed during one treatment setting using a combination CT-fluoroscopy hybrid imaging equipment with embolization, percutaneous cryoablation, and cementoplasty. Initial treatment of embolization provided pain palliation and decreased bleeding risk for subsequent cementoplasty (**b**, frontal fluoroscopic image during injection of the internal iliac artery with black arrows outline hypervascular osseous tumor blush). Percutaneous cryoablation was performed immediately afterwards for local tumor control and additional pain palliation (**c**, procedural axial non-contrast CT with white arrows outlining cryoablation therapeutic ice ball). Lastly, cementoplasty was performed to consolidate the unstable superior acetabulum in order to improve weight bearing capability (**d**, frontal pelvic radiograph with white arrows identifying cement within the superior acetabulum above the hip arthroplasty)

3 Materials

The two main types of bone cement are polymethyl methacrylate (PMMA) and calcium phosphate. PMMA is the most commonly used cement, due to a high compressive strength and the non-biodegradable property. The physical qualities of the PMMA are thought to provide pain relief through durable resistance to compression forces, self-adhesive entrapment of small fracture fragments, and exothermic destruction of nociceptive pain fibers that occurs during cement polymerization (Wang et al. 2012). Calcium phosphate cements are derived from hydroxyapatite (HA). Compared to PMMA, HA cements have lower compressive strength, a longer time to primary hardening, and are often biodegradable and osteoconductive (Kurashina et al. 1995). Calcium phosphate cements can be used for osteoporotic vertebral body fractures to minimize fractures of adjacent levels, and for children or young adults where cement absorption is desired in anticipation of normal osteoclastic activity and bone regrowth.

Bone access needles are durable cannulated needles that typically range between 10 and 15 gauge with needle length 10 and 15 cm. Usage of the largest diameter needle safely possible will optimize the flow of the cement according to Poiseuille's law, which proves pressure and flow rate will be decreased with cement injected through a larger diameter needle. The shortest needle that can reach the location of interest will minimize premature hardening of the cement during injection. In regard to needle tip shapes, the majority of needles come with either a diamond tip for a straight and true access or a beveled tip that allows more directional steerage during advancement. Steerable, articulating, and preformed curved needles are also available. In osteoporotic bone, manual pressure is often sufficient to advance the needle into the location of interest. Mallets may be useful in normal density bone. Small battery powered drills can be applied for added speed or to advance across thick osseous cortex or sclerotic metastases.

The injection of cement may be performed using a multipurpose 1 mL syringe or through the use of a mechanical injector that has been manufactured specifically for cement injection. Mechanical injectors can facilitate cement delivery in small measured increments and allow controlled advancement of viscous cement. Before injection, high-pressure balloon catheters and curved stylets can be advanced through the bone access needle to sculpt a cavity and further improve controlled cement distribution. Similarly, several osseous implants have been advanced to provide a mechanism to create a means to improve controlled cement delivery.

4 General Technical Considerations

Percutaneous cement injection is not without technical challenges. Preprocedure evaluation of imaging and clinical factors can identify pitfalls. Cortical defects from fractures or tumor erosion can predispose for cement leakage, and consequently limit consolidative effect. Epidural tumor extension or fracture fragment protrusion into the spinal canal through a disruption in the posterior vertebral body wall are relative contraindications to vertebral augmentation. Tumor extension through a pedicle may hinder safe access under fluoroscopic guidance, although CT guidance can be used to overcome this challenge. Lastly, the presence of an active infection should be excluded before injection of cement.

Procedural complications can also be avoided by careful planning from initial procedural imaging. Needle approach should avoid nerves, tendons, and arteries to minimize traumatic complications. In cancer patients, needle trajectory should to avoid passing through tumor in order to prevent tract seeding upon needle removal (Lee et al. 2014). The choice of image guidance modality is operator dependent based on preference and availability, but should provide visualization of the osseous margins. For out of plane needle insertion, needle guidance software may be helpful. When multiple needles are required during the same treatment session, the needle orientation, and entry sites can be spaced to avoid needle hub crowding, which can be particularly problematic during multilevel vertebroplasty or large volume cementoplasty that may require multiple needles to be placed in close proximity.

Lastly, realistic expectations should be set for the patient's post-procedure recovery and pain relief. A post-procedure recovery period of 1–2 hours is typical, with same day discharge or one night extended recovery determined by the patient's baseline condition and degree of debilitation. As the cure time for PMMA cement is within an hour, patients may bear weight shortly after the procedure. This recovery period may be delayed for calcium phosphate cement, which has a longer cure time than PMMA. The original mechanical pain is typically relieved after the cement has cured although the palliative effects might not be fully appreciated due to the procedure-related soreness that normally resolves 1–7 days after the procedure. Physical therapy should be encouraged to overcome physical deconditioning. A post-procedure telephone or clinic follow-up after 1–2 weeks can ensure appropriate pain relief and confirm absence of procedure-related complications. Recurrent pain in the region of treatment should raise concern for incomplete consolidation, progression of fracture, or a new fracture in an adjacent bone.

5 Vertebral Augmentation

Vertebral augmentation encompasses the treatments of vertebroplasty and kyphoplasty (Fig. 2). Vertebroplasty describes the injection of cement into the vertebral body to provide palliation of a painful compression fracture and to prevent further loss of vertebral body height (Anselmetti et al. 2012; Gangi et al. 2003). Kyphoplasty undertakes the additional step of restoring vertebral body height to reduce kyphosis before cement injection (Berenson et al. 2011). The most common height restoration technique

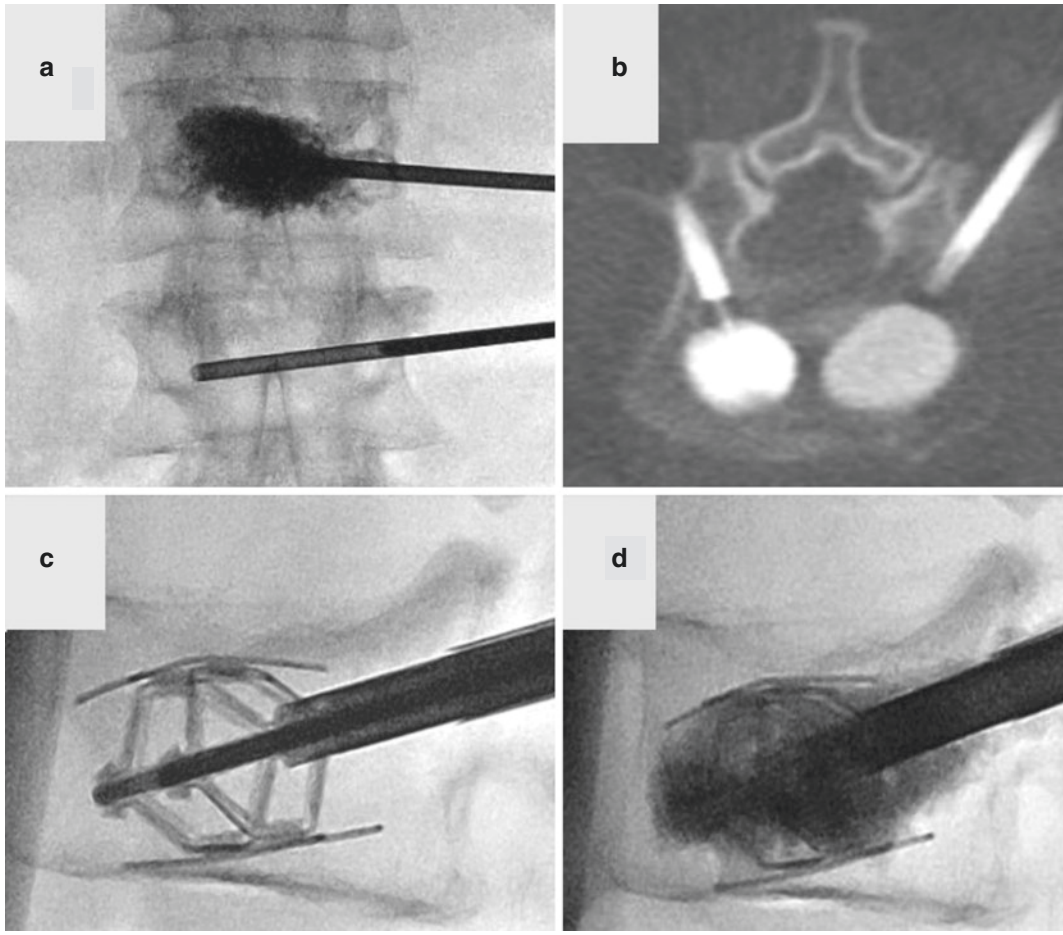

Fig. 2 Fluoroscopic-guided two level vertebroplasty with right unipedicular access at both levels (**a**). CT-guided bipedicular kyphoplasty with balloon catheters inflated with dilute contrast (**b**). Fluoroscopic-guided bipedicular kyphoplasty with expandable devices before and after PMMA injection (**c** and **d**, respectively)

employs the use of an inflatable balloon catheter that is passed through the bone access needle to lift the vertebral endplate and create a cavity that will subsequently be filled with cement.

Both vertebroplasty and kyphoplasty have documented benefits for vertebral body fractures caused by either osteoporosis or malignancy (Filippiadis et al. 2017; Santiago et al. 2014). Outcomes include significant pain reduction, decreased analgesic use, and improvement in disability scores. Durability of pain relief may be greater for pathologic fractures compared to osteoporotic fracture (Pron et al. 2016). The application of vertebroplasty versus kyphoplasty is at the discretion of the operator and may depend upon degree of vertebral body compression and the presence of tumor extension through the posterior vertebral body into the epidural space.

Several osseous implants have been developed specifically for use in the kyphoplasty (Noriega et al. 2015; Anselmetti et al. 2013). These implants can provide some structural support, expand the vertebral endplates, and improve the controlled injection of cement. The bone access needles for these devices are typically larger in

diameter than 10 gauge, and thus the size of the vertebral pedicle should be carefully measured before beginning the procedure.

6 Cementoplasty: Outside of the Spine

Outside of the spine, cementoplasty can relieve pain when applied for appropriately selected patients (Fig. 3) (Anselmetti et al. 2008; Anselmetti 2010; Sun et al. 2014). The most common application for cementoplasty is in the load bearing portions of the pelvis, specifically the superior acetabulum and sacrum. Cementoplasty in the acetabulum can also be referred to as acetabuloplasty, while sacral cement injection is referred to as sacroplasty. While the sacrum is subjected to some torque stress, the predominant force is unidimensional. The access to the unstable bone should avoid joint and neuropathic trauma and facilitate the injection of cement throughout the defect or fracture.

Cement injection can also provide some pain relief in the stabilization of flat and long bones although the effect is not as complete in these locations given the multidimensional torque stresses that are experienced. The mechanism of palliation is more reliant on the consolidation small fracture fragments and the exothermic destruction of nociceptive pain fibers in the periosteum (Urrutia et al. 2008; Anselmetti et al. 2009). When possible, the insertion of metallic screws may improve durability for unstable fractures or large lytic defects in these locations (Deschamps et al. 2016). For example, the cementoplasty of femoral neck defects and fractures is routinely accompanied by screw fixation (Tian et al. 2016).

7 Complications

Complications from cement consolidation techniques can be attributed to traumatic injury from needle trajectory, extraosseous cement leakage into surrounding soft tissues, intravascular cement emboli, displacement of bone marrow with fat emboli, and transient cardiovascular reaction to cement (Yevich et al. 2018). Understanding potential complications optimizes patient selection, improves technique, and guides post-procedure management.

Cement leakage outside of the osseous margins can cause symptoms from direct compression or inflammation of adjacent nerves or muscle fibers (Fig. 4) (Hildalgo et al. 2012). Clinical sequela can be minimized with slow and controlled cement injection with early intraprocedural detection of leakage by imaging. Small amounts of cement leakage into the intervertebral disc space are typically asymptomatic (Mirovsky et al. 2006; Lin et al. 2004). Similarly, a small amount of leakage into a joint space is likely of little clinical consequence, however, may result in inflammation of the joint capsule or subchondral erosion. Cement leaked into adjacent muscles may cause persistent inflammation with muscle activity. Treatment of cement leakage is

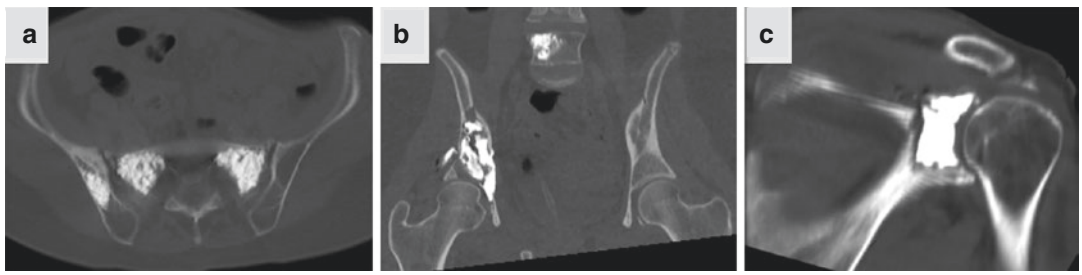

Fig. 3 CT-guided cementoplasty for the right iliac bone and bilateral sacral alae for metastatic breast cancer (**a**). CT-guided right acetabuloplasty and L5 vertebroplasty for metastatic sarcoma destruction (**b**). CT-guided cementoplasty of a pathologic lytic defect in the scapular neck and glenoid (**c**)

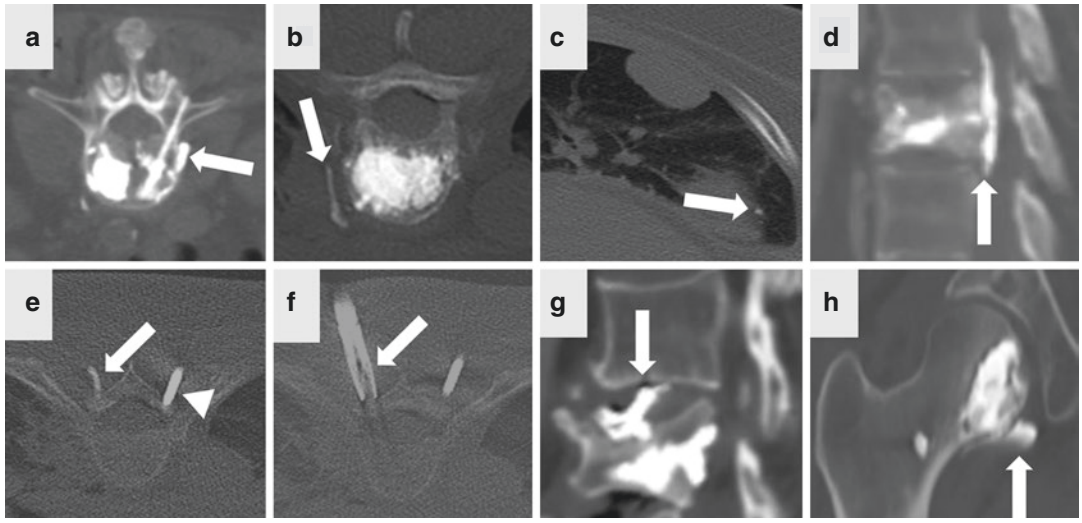

Fig. 4 Multiple CT images after cement injection demonstrating leakage of PMMA from the osseous margins into the perivertebral soft tissues (**a**, arrow), into the periosteal venous plexus (**b**, arrow) with small non-significant cement pulmonary embolus (**c**, arrow), into the spinal canal (**d**, arrow), into the erector spinae muscle (**e**, arrow identifies retained cement fragment after removal of left pedicular access needle while arrow head identifies the contralateral needle still in place) causing significant focal point tenderness necessitating subsequent removal with forceps (**f**, arrow), into the intervertebral disc (**g**, arrow), and into the inferior aspect of the hip joint (**h**, arrow)

typically conservative with non-steroidal anti-inflammatory agents or steroids. Decompression or cement retrieval may be required in patients with unrelieved pain caused by inflammation and irritation of a nerve or muscle by a cement leakage outside of the osseous margins (Barragan-Campos et al. 2006).

Cement extrusion into the peri-osteal vasculature is another source of complication. Cement passage into the periosteal venous plexus has a reported incidence up to 25% (Pitton et al. 2008; Venmans et al. 2010). Pulmonary cement emboli can be avoided if venous leakage is identified early and injection is stopped. Small, isolated cement emboli are typically asymptomatic and do not require any treatment. Rarely, venous cement emboli can cause grave consequences that include cardiopulmonary sequela from large pulmonary emboli (Tozzi et al. 2002; Padovani et al. 1999; Monticelli et al. 2005), cardiac perforation from a needlelike cement embolus (Kim et al. 2005), and paradoxic cerebral arterial embolization. Intra-arterial cement extrusion is another rare, but potentially serious complication (Chung et al. 2005). Possible predisposing risks include a highly vascular malignant osseous lesions with arterio-venous shunting, needle tip positioned in close proximity to an artery, and higher pressure cement injection. The addition of radiofrequency ablation immediately before cement consolidation of vascular bone malignancy may decrease the incidence of vascular cement leakage (David et al. 2017).

Lastly, cement displacement of bone marrow can result in transient cardiovascular changes and pulmonary fat embolism (Aebli et al. 2002; Ahmed et al. 1993). In patients with a large volume fat embolus, symptoms that include respiratory insufficiency, neurologic manifestation, and petechial rash can develop 12–72 h after the procedure (Uransilp et al. 2018). Treatment includes supportive measures with oxygenation and a short course of steroids. In the prevention of symptomatic fat embolisms, recommendations include limiting cement injection volume to less than 30 mL in one setting (Heini and Orler 2004).

8 Conclusion

Cement consolidation is a minimally invasive palliative procedure that can be performed inside and outside of the spine to stabilize weakened or fractured bone secondary to either osteoporosis or tumor erosion. Appropriate patient selection relies on image correlation of an osseous defect with a source of mechanical pain. Cementoplasty is most appropriate to stabilize in locations under unidimensional axial weight-bearing forces, such as in the vertebral bodies and acetabulum, but may also be performed in long and flat bones with some degree of palliative effect. In the case of malignancy, the durability of cement consolidation can be improved with a comprehensive treatment with other techniques such as ablation, embolization, and screw fixation.

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Palliative Bone Tumors Thermal Ablation

Roberto Luigi Cazzato, Julien Garnon, and Afshin Gangi

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Abstract

New minimally invasive heat- or cold-based techniques allow percutaneous image-guided tumor destruction. Their application in bone has progressively gained ground in the last few decades, with a major role played for the treatment of painful bone tumors.

The aim of this chapter is to present all the different ablative techniques available, their advantages and disadvantages as well as the strategies to be followed for their application in cancer patients presenting with painful bone tumors.

R. L. Cazzato (✉) · J. Garnon · A. Gangi
Department of Interventional Radiology, University Hospital of Strasbourg, Strasbourg, France
e-mail: Roberto-luigi.cazzato@chru-strasbourg.fr; Julien.garnon@chru-strasbourg.fr; Afshin.gangi@chru-strasbourg.fr

1 Introduction

Thermal ablation is applied to achieve tumor destruction through the use of heat- or cold-based energies (Cazzato et al. 2015, 2016a, 2019; Barile et al. 2017, 2018; Gangi et al. 2010; Tsoumakidou et al. 2016a), delivered percutaneously in most of the cases, unless High-Intensity Focused Ultrasound (HIFU) is used.

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_9

When heat-based techniques are used, the target tumor undergoes coagulative necrosis; on the other hand, when cold-based energy is used (i.e., cryoablation—CA), the mechanism underlying the cellular death is much more complex and still not completely understood, especially due to the involvement of an anti-tumor cryo-immunologic effect (Cazzato et al. 2016a; Rauch et al. 2017).

In this chapter, the most common ablative techniques applied for the palliative management of painful bone tumors will be described, and their advantages and disadvantages presented; in the end, the strategies guiding their applications and the relative results will be outlined.

2 Palliative Bone Ablation in Cancer Patients

Palliative ablation may be proposed to cancer patients presenting with bone tumors in order to:

- Control one or few focally painful bone tumors—In this perspective, the culprit tumor should be clearly identified on the most recent cross-sectional imaging available; and clinically identified as the real source of the focal pain, which should be moderate/severe (≥4/10 on a 0–10 visual analogic scale over the 24 h). In case of a painful lytic bone lesion, the ablation should ideally target the interface between the normal bone and the tumor where pain generates; nevertheless, whenever possible, complete tumor destruction should be attempted.
- Achieve tumor debulking—in this perspective, ablation is applied mostly to control the pain related to bone tumor infiltrating the surrounding soft tissues or to prevent complications related to the growth of the target tumor (e.g., tumor of the vertebral body undergoing ablation to prevent spinal cord compression).

In both cases, mainly metastatic bone tumors rather than primary bone sarcomas are treated.

Following ablation, bone consolidation should be always considered in order to prevent a secondary bone insufficiency fracture. In this perspective, two percutaneous techniques are available: osteoplasty and osteosynthesis that may be used alone or in combination just after ablation. The selection between these two techniques is done based on the features of the target tumor and the predominant biomechanics of the target bone (Cazzato et al. 2019). In particular, osteoplasty is used when a lytic tumor is noted in bones mainly subjected to compressive stress (e.g., vertebral body and acetabulum) (Gupta et al. 2012; Lane et al. 2011; Weill et al. 1998; Tsoumakidou et al. 2017). Osteosynthesis is mainly used to stabilize impending or pathologic/bone insufficiency fractures of the pelvic ring (including the femoral neck if no extensive articular or cortical involvement, especially of throcantheric region is noted) or of the scapula (Cazzato et al. 2016b, 2017; Garnon et al. 2016), provided a contraindication to surgery. However, it should be noted that in multi-metastatic patients presenting with a simple focal mechanic pain related to a bone metastasis complicated by an impending or a pathologic/bone insufficiency fracture, simple osteoplasty, or osteosynthesis might be enough to achieve effective pain relief.

Absolute contraindications to ablation (and to bone consolidation) include irreversible coagulation impairment and local/systemic infections.

3 Ablative Techniques

Laser—Lasers are used to deliver an electromagnetic energy in the infrared wavelength (805 nm). The laser energy is delivered through a thin and flexible optic fiber (400 micron) that is coaxially deployment through an 18G needle. The ablation area provided by a single laser fiber is oval and in bone hardly exceeds 16 mm in the small axis when the continuous ablation mode (2 W) is used (Gangi et al. 1997). Moreover, once the total amount of delivered energy reaches the cut-off of 1000–1200 J, no further increase in size of the ablation area is achieved. For this reason, when large areas of ablation are needed, multiple fibers are applied with a final synergistic effect, even though the final size of the ablation zone rarely exceed 2–3 cm (Gangi et al. 2010; Gangi and

Buy 2010). Nevertheless, application of more than two fibers is deemed unpractical, and for this reason in current clinical practice, laser ablation is limited to the treatment of small, painful bone tumors such as the osteoid osteoma, which needs a small ablation of the nidus that generally measures less than 1 cm (Gangi et al. 2007; Tsoumakidou et al. 2016b).

Radiofrequency ablation (RFA)—RFA has been one of the first techniques applied to treat bone tumors (Cazzato et al. 2018a). RFA achieves an effective coagulative necrosis of the target tumor through ionic agitation (i.e., frictional heating) induced by an electric current flowing between the electrode deployed inside the tumor and some grounds pads attached on the tight of the patient (i.e., monopolar system); or between two electrodes deployed one next to the other, or two dipoles localized at the distal tip of the same electrode (bipolar systems). Since the frictional heating depends on the availability of ionic molecules (i.e., water) in the target tumor, RFA is not the best technique to be applied in heavy osteoblastic tumors; in such cases, high impedance (i.e., tissue resistance in receiving the electrical current) is noted and effective energy deliver to the tumor does not occur. Most of the RFA electrodes are cooled with cold saline to avoid tissue carbonization around the active tip of the electrode with the aim of reducing impedance, thus enlarging the ablation zone. Nevertheless, RFA cannot achieve ablation zones that exceed 3–4 cm.

Since the electric current flows in the body of the patient, RFA is not recommended in patients who had previously received the implantation of electric devices such as cardiac pacemakers. This contraindication is particularly factual for unipolar RFA systems. On the contrary, bipolar systems may be ideally used in patients carrying an implantable electric device since the electrical current does not flow in the body of the patient; nevertheless, all manufacturers discourage the use of these systems for security reasons in patients carrying an electric implantable device.

The main advantage of bipolar systems compared to unipolar ones is that the ablation zone granted by the former is smaller and more predictable; for this reason, bipolar systems are specifically used to perform spinal ablations (Cazzato et al. 2018b).

MicroWave Ablation (MWA)—MWA has been recently used to treat bone tumors (Pusceddu et al. 2013). MWA applies electromagnetic energy delivered percutaneously through an antenna. Such energy induces molecular agitation and subsequent tissue heating. The main advantage of MWA compared to RFA is that MWA energy can radiate through all biological, including cortical bone and charred tissues, and enables faster and larger ablation zones (up to 4–5 cm when 2–3 antennas are activated simultaneously). First-generation antennas presented several limitations mainly dealing with the oval-shaped morphology and the relatively unpredictable extension of the ablation zone. Nevertheless, these drawbacks are now overcome with new antennas that provide more spherical and predictable ablation areas (Saccomandi et al. 2015).

Cryoablation (CA)—CA uses cold (up to −140 °C at the tip of the probe and up to 0° on the edge of the ablation zone—i.e., iceball) temperatures to destroy tumors (Cazzato et al. 2016a; Hinshaw et al. 2014). The iceball is generated at the tip of 15–17G cryoprobes provided of a decompression compartment where specific gases (i.e., argon and helium) can flow. Rapid argon decompression results in iceball growth; on the contrary, when helium is applied, the iceball melts (i.e., active thawing). New generation cryoprobes apply electrical current rather than helium to achieve the active thawing. Usually, a double 10-min freeze cycle interrupted by an 8–10 min. thaw is the classic protocol of ablation, which achieves cellular death through mechanical damage to cellular membranes produced by ice crystals, osmotic changes into the tissue, endothelial injury, ischemia, and a complex and still not completely understood cryo-immunological effect.

The main advantages of CA are: (a) precise control of the iceball with cross-sectional imaging (especially CT and MRI) (Fig. 1); (b) simultaneous and synergic multiple-probe ablation allowing iceball shaping according to the morphology of the target tumor; (c) possibility of

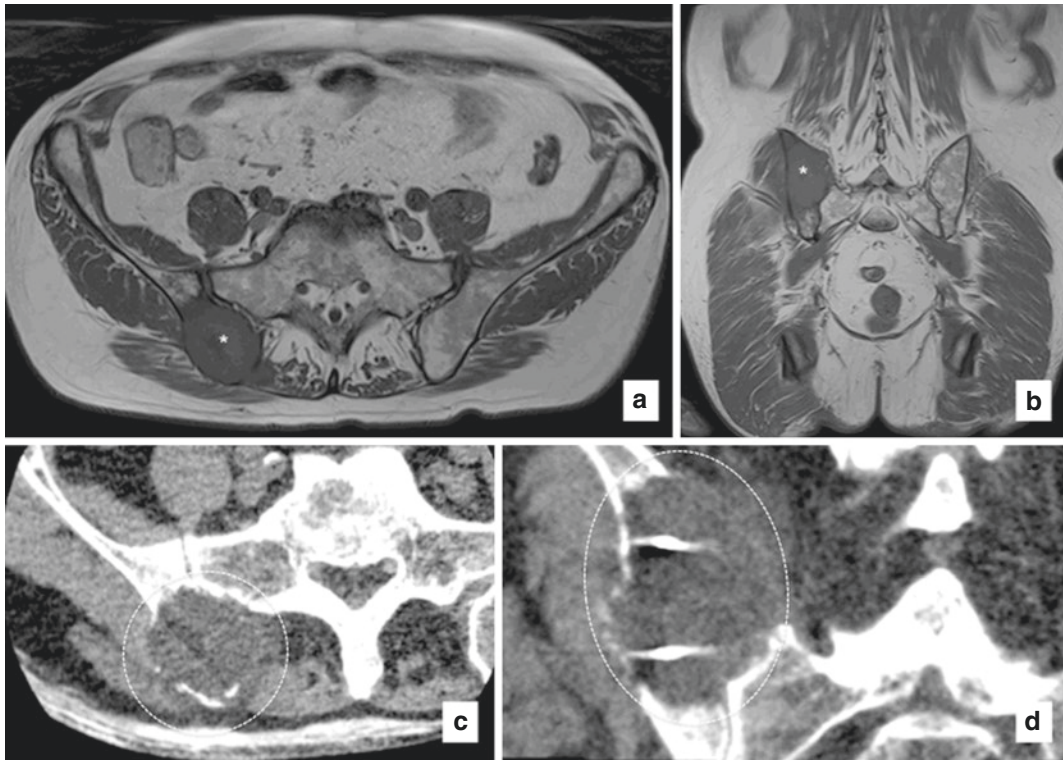

Fig. 1 Axial (**a**) and coronal (**b**) T1-weighted sequences showing a painful lytic metastasis (*) of the right iliac bone. The tumor was treated with two cryopobes under CT-guidance, which granted (**c**, **d**) a clear visualization of the hypodense iceball (dotted circle)

treating osteoblastic bone tumors since the iceball goes across the blastic bone and cortical bone (Fig. 2); (d) relatively painless procedures since the iceball has intrinsic anesthetic properties. As a result, CA is particularly indicated for the treatment of bone tumors and in particular for the soft-tissue component of bone tumors. Nevertheless, it should be noted that CA is expensive, time-consuming and requires experienced operators especially when many probes are activated simultaneously.

High-Intensity Focused Ultrasound (HIFU)—HIFU is a scalpel-free heat-based technique. It is centered on the focalization of an ultrasound beam on the target tumor. The beam is generated by a transducer placed on the skin of the patient (Napoli et al. 2013a), passes inertly through tissues, and is focused on the target tumor—generally identified by means of MRI-guidance—where the mechanical energy of the ultrasound beam is converted into thermal energy. When the technique is guided with MRI, a real-time monitoring of the temperature reached within and around the tumor is possible.

The ultrasound beam does not go through the cortical bone; as a result, if the ultrasound beam is focused on bone cortex, a periosteal burning is achieved; and mechanism such as this represents the core of the treatment of painful bone metastases presenting with a cortical overlay. For the same reason, deep bone lesions located beyond the cortical bone cannot be directly treated with HIFU, which is also not currently available for spinal interventions (Huisman et al. 2015). Other drawbacks include the limited availability of the technique, the long procedural time, and the contraindications in patients who cannot undergo MRI.

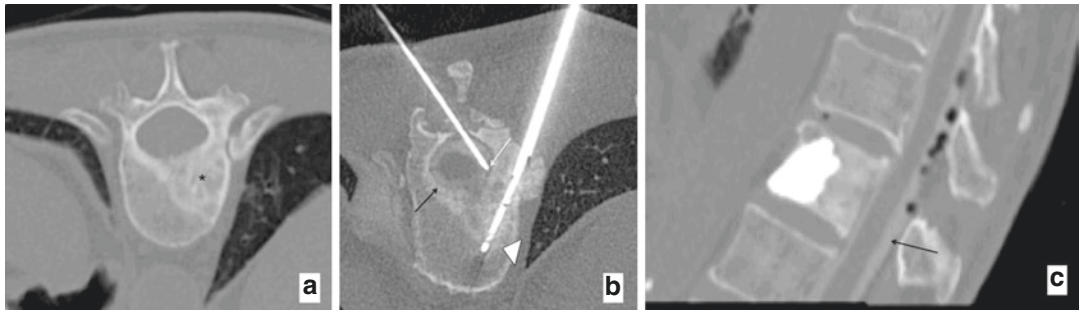

Fig. 2 Axial (**a**) CT image showing a painful sclerotic metastasis (*) of Th12. (**b**) The tumor was treated with a single cryoprobe (arrow head; the iceball is not seen since it did not extend beyond the cortical bone); and hydrodissection of the epidural space (black arrow) coupled to thermal monitoring (white arrow) were also applied. (**c**) In the same session, vertebroplasty was performed 15 min after the end of cryoablation to avoid secondary vertebral collapse

4 Protective Measures

Although bone thermal ablation is considered a safe procedure, it should be noted that the most common complications are mainly related to the unintentional heating/freezing of non-target organs lying in proximity of the target tumor. Accordingly, the type and grade of complications mainly depend on the loco-regional anatomy. In this perspective, accidental nervous injuries represent one of the most common and worrisome complications since many nerves are not clearly seen on common cross-sectional imaging. Moreover, particular attention should be paid to the skin when performing ablation of superficial bone tumors.

Therefore, careful knowledge of the regional anatomy and planning of the procedure are mandatory to identify all the structures at risk, including nerves, cartilages, and skin; and all the required protective measures needed to avoid iatrogenic complications. Patients should be carefully instructed about all the possible ablation-related risks.

Several different protective measures exist and should be adopted in order to protect nearby non-target structures (Fig. 2), especially if it is estimated that the non-target structure lies less than 10 mm from the presumed external border of the ablation area (McMenomy et al. 2013; Tsoumakidou et al. 2011). Common protective measures may be divided into two main categories:

4.1 Techniques Achieving Physical Displacement

(a) Of the target tumor (i.e., iceball retraction through a gentle withdrawal of the cryoprobe during CA)
(b) Physical displacement of the non-target structure through the interposition of fluids (i.e., saline), gases (CO^2), or angioplasty balloons. In such a case, injection of liquids such as the saline, has the great advantage that depending on the temperature of the injected liquid, warming-up or cooling-down of the non-target structure is possible during the ablation.

Liquids injection into the subcutaneous tissue is also used, often in combination with sterile gloves filled with cold/hot saline to protect the skin when superficial bone tumors are treated.

In case of RFA application, 5% electrically inert dextrose solution should be used in place of 0.9% saline. In the end, when CT-guidance is used, 5–10% contrast medium dilution may be useful to increase the visualization and the extension of the hydro-displacement.

4.2 Morphological/Functional Monitoring

(a) CA allows an easy visualization of the iceball with common imaging modalities.

Nevertheless, it should be noted that in case of bone ablation, when CT-guidance is used, the visualization of the iceball might be problematic until the iceball extends beyond the bone into nearby soft tissues.

(b) Thermometers (i.e., thermocouples or fiber-optic sensors) can be deployed to monitor the temperature in close proximity of the nearby non-target structure. In the specific case of nerves, the target temperature should be within a fixed physiological range (10–45 °C); and if such range is overcome, ablation should be immediately stopped.

(c) Nervous function can be monitored during ablation through electrostimulation or somatosensory-evoked potentials.

All the aforementioned measures can be applied alone or in combination.

5 Results

A growing number of studies provided evidence that ablation is fast and effective in achieving pain relief in patients presenting with painful bone tumors. On average, pain relief is experienced in 85% patients (range 69–100%; mean pain drop on the O-10 VAS: 5.5) at mean 3.2 months follow-up (range 1–6) (Table 1).

At the moment, the largest experience has been obtained with RFA and CA. Nevertheless, the recently introduced MWA and HIFU have also proved their efficiency in achieving pain relief. Moreover, given the "non-invasive" profile of HIFU, it is likely that a prominent number of patients in the near future will benefit more from this technique. Nevertheless, it has been highlighted that the number of patients that may benefit from HIFU may significantly increase if such technique is combined to percutaneous protective measures (Bing et al. 2018).

The rate of major complications following palliative ablation of bone tumors is generally low (5–6%) (Cazzato et al. 2018b; Goetz et al. 2004; Dupuy et al. 2010; Callstrom et al. 2013; Prologo et al. 2014). The most commonly reported major complications include secondary fractures, neuropathies, pain, and infections/osteomyelitis. Among all these complications, fracture and irreversible neuropathies are the most worrisome events, even though they may be

Table 1 Results of palliative ablation of painful bone tumors. NR: Not reported; RFA: Radiofrequency Ablation; CA: Cryoablation; MWA: Microwave ablation; HIFU: High Intensity Focused Ultrasound

Paper	Ablation modality	No. patients (No. tumors)	Mean pain Score change	% patients With reduced pain	Follow-up (months)
Goetz et al. (2004)	Monopolar RFA	43 (43)	7.9–1.4 (6.5/10)	95%	6
Dupuy et al. (2010)	Monopolar RFA	55 (55)	NR (14.2/100)	NR	3
Wallace et al. (2015)	Monopolar RFA	72 (110)	8.0–2.9 (5.1/10)	78%	1
Baagla et al. (2016)	Bipolar RFA	50 (69)	5.9–2.1 (3.8/10)	70%	3
Cazzato et al. (2018b)	Bipolar RFA	11 (11)	7.8–1.1 (6.7/10)	100%	1.9
Callstrom et al. (2013)	CA	61 (69)	7.1–1.4 (5.7/10)	69%	6
Prologo et al. (2014)	CA	50 (54)	8–3 (5/10)	94%	3
Pusceddu et al. (2013)	MWA	18 (21)	5.6–0.5 (5.1/10)	94%	3
Kastler et al. (2017)	MWA	16 (16)	NR	94%	1
Liberman et al. (2009)	HIFU	31 (32)	5.9–1.8 (4.1/10)	72%	3
Napoli et al. (2013b)	HIFU	18 (18)	7.1–1.1 (6/10)	88.8%	3

considered predictable thus, warranting for the adoption of adequate preventive measures (i.e., bone consolidation following ablation especially in bones subjected to intense biomechanical stress; and protective measures to avoid iatrogenic injuries to non-target structures).

6 Advantages of Ablations

Nowadays, radiation therapy (RT) represents the gold-standard for the treatment of painful bone metastases (Lutz et al. 2017); nevertheless, many patients experience partial or even no pain relief. When pain relief occurs after RT, it generally takes 3–4 weeks to occur after the end of the treatment; and when pain recurs, patients may be not retreated if the maximal radiation dose has been already delivered on the target area; or if a patient can be retreated with RT, partial or complete pain relief will occur in only half of the retreated cases (Lutz et al. 2017). In the end, although pain relief and local tumor control granted by the new stereotactic body RT (SBRT) are improved (50% of complete pain relief; 90% local tumor control at 1 year (Husain et al. 2017)) compared to the standard external beam RT (EBRT), a high rate of secondary bone insufficiency fractures is expected to occur (in spinal series, up to 1/3 treated vertebral levels) (Husain et al. 2017).

Compared to the RT, ablation yields all the following advantages:

- Faster pain relief (7–10 days from the end of the treatment)
- No limit to the number of ablative treatments that can be performed on the same tumor
- Possibility to combine bone consolidation to ablation in the same interventional session thus, preventing the risk of secondary bone insufficiency fractures (Fig. 2)

Despite all the advantages showed by percutaneous ablation over RT, it should be noted that when both these treatments are applied on the same target tumor, a synergic effect is noted in terms of pain relief. In this perspective, Di Staso et al. (2011) compared the palliative effects of RT vs RFA combined with RT; they found that the group receiving the double treatment experienced a significantly higher rate of complete and overall pain relief at 3-month follow-up (53.3% vs 16.6%, and 93.3% vs 59.9%, respectively). Moreover, recurrent pain was more common after RT alone (26.6%) than after RFA and RT (6.7%). Interestingly, the group receiving the combined treatment did not face higher morbidity as compared to the group receiving RT alone. The same team proved also that the addition of RT to CA significantly improves the rate of complete pain response compared to CA alone (Di Staso et al. 2015).

Similarly, a systematic review about spine RFA confirmed such results and showed also that the best pain management is achieved in patients receiving RFA, vertebroplasty, and RT on the same vertebral level (Cazzato et al. 2018a).

7 Conclusions

Several different heat- or cold-based techniques can be applied to treat focal pain originating from bone tumors; and progressively growing evidence is supporting such relatively new techniques in clinical practice. The main advantages of these techniques are fast pain relief, the possibility to repeat the treatment in case of recurring pain, the possibility to grant bone consolidation during the same interventional session, and the synergic effect with all the other medical and surgical tools available for the treatment of bone tumors, with a specific regard for RT.

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Part III

Neurological Pain Relief Solutions

Epidural Steroid Injections

Ashutosh Joshi and Wern Hsien Bin

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Abstract

Epidural steroid injections are the most widely utilized pain management procedure in the world. Delivering high concentration of corticosteroids directly in the area of inflamed nerves appear to provide some pain relief and functional improvement.

A. Joshi (✉) · W. H. Bin
Department of Anaesthesia,
Khoo Teck Puat Hospital, Singapore, Singapore
e-mail: Ashutosh.Joshi@ktph.com.sg;
Bin.Wern.Hsien@ktph.com.sg

© Springer Nature Switzerland AG 2021
P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_10

In this chapter, overview of epidural steroid techniques, indications, contraindications, and complications are discussed. These injections can also be utilized for the management of severe neuropathic symptoms including allodynia and hyperalgesia in the setting of cancer pain and palliative care.

1 Introduction

Epidural steroids are one of the most commonly performed procedures in pain medicine. The cervical and lumbar epidural spaces can be accessed using multiple approaches including interlaminar, transforaminal, and caudal. The purpose is to deliver higher concentrations of corticosteroid directly in the area of an inflamed nerve root. Corticosteroids inhibit the enzyme phospholipase A2, which is itself an inflammatory mediator present in elevated concentrations in herniated and degenerative intervertebral disks (Saal 1995). However, its main role is as the rate-limiting factor involved in the production of arachidonic acid, which is the principal substrate for the cyclo-oxygenase and lipo-oxygenase pathways. Metabolism by these pathways results in the formation of prostaglandins, prostacyclins, thromboxanes, and leukotrienes. Prostaglandins, along with these other arachidonic acid by-products, can cause or exacerbate pain via their inflammatory effects and the ability to sensitize peripheral nociceptors (Petho and Reeh 2012). In addition to their anti-inflammatory effects, steroids may inhibit pain via their ability to suppress ectopic discharges from injured nerve fibres (Devor et al. 1985) and depress conduction in normal unmyelinated C fibres (Johansson et al. 1990). Several proposed mechanisms include local anaesthetic's pain relieving properties as well. The injection of local aesthetic can increase blood flow to ischemic nerve roots (Kobayashi et al. 2010) and, similar to steroids, suppress ectopic discharges from injured neurons and slow or halt nociceptive transmission (Devor et al. 1992).

2 Anatomy of the Epidural Space

The epidural space starts at the point where the periosteal layer of the foramen magnum comes together with the dura. The inferior boundary is at the sacrococcygeal membrane, the anterior boundary is the posterior longitudinal ligament, the posterior boundary is the ligamentum flavum, and the lateral boundaries are the pedicles and the intervertebral foramina. The space contains fat, lymphatics, and venous plexus. The ligamentum flavum is thin in the cervical region and thickens as you move caudal (Waldman 2007a). In the cervical region, the distance between the ligamentum flavum and the dura is 1.5–2 mm at C7 (due to cervical enlargement) as opposed to the lumbar region where at L2, it is 5–6 mm.

3 Cervical Epidural Injections

There are two approaches to access the cervical epidural space: interlaminar and transforaminal. There are no studies that have shown that one is better than the other; however, complications associated with each are significantly different (Van Zundert et al. 2009). A systematic review concluded that interlaminar cervical epidural injections provide a significant effect on cervical radicular pain (Benyamin et al. 2009).

3.1 Indications

Common indications for cervical epidural injections are:

- Cervical radiculopathy
- Cervical degenerative disk disease
- Cervical disk herniation
- Cervical spinal stenosis
- Cervical postlaminectomy (failed neck) surgery syndrome
- Cervical vertebral compression fractures
- Postherpetic neuralgia/herpes zoster
- Cancer-related pain

3.2 Contraindications

Absolute: unwilling patient, localized infection over procedure area, current anticoagulant use, increased intracranial pressure (ICP), bleeding diathesis, and patient that cannot remain still during the procedure.

Relative: allergy to medications that will be injected (contrast, local anaesthetic, steroid) pregnancy, immunosuppression, systemic infection, and anatomic changes that would prevent a safe procedure (congenital or surgical).

3.3 Cervical Epidural Transforaminal Epidural

3.3.1 Injection Technique

All patients should be fully monitored, and equipment to handle airway, local anaesthetic toxicity, and cardiovascular emergencies should be readily available. After discussing risks and benefits, answering questions, and obtaining written informed consent, an intravenous line is placed (for sedation or for emergency access). The patient is taken into the procedure suite and can be placed in the supine or lateral position depending on physician preference. The area of the neck is prepped and draped in a sterile manner. The fluoroscopy beam is then adjusted to visualize the intervertebral foramen at its maximum diameter, usually an anterior oblique view (Fig. 1a). The anterior surface of the superior articular process of the inferior vertebrae (posterior aspect of foramen) is identified, and the entry point is marked. The skin and subcutaneous tissues are anaesthetized with 1% lidocaine.

A 25-gauge needle is then directed toward the anterior portion of the superior articular process (Fig. 1b). It should always be directed toward this bony landmark, as going directly toward the foramen could result in a needle being placed too deep and into the spinal cord. Once the superior articular process is contacted, the depth of the needle should be noted. Repositioning of the needle should never exceed this noted depth by more than a few millimetres. The needle is then carefully adjusted so that it passes into the intervertebral foramen. The needle should always remain slightly anterior to the superior articular process. It should never be in the anterior portion of the intervertebral foramen as this may risk injection into the vertebral artery. Once the needle is in the correct position, the fluoroscope is repositioned for a true anteroposterior (AP) view. This will allow the physician to see the depth of the needle. The correct depth is when the tip of the needle lies opposite the sagittal midline of the silhouettes of the articular pillars. If the needle contacts the existing nerve root, the patient will feel radicular pain. At this point, the needle should be slightly withdrawn and the procedure halted until the sensation disappears. If the sensation does disappear, the needle can be redirected back to its intended position, but avoiding the exact spot that caused the radicular pain. Fluoroscopy should be used to check in an oblique direction as well as an AP view to confirm needle position and depth. After negative aspiration is confirmed, less than 1 mL of contrast solution is injected under live fluoroscopy (Fig. 1c). It should enter the intervertebral foramen and outline the spinal nerve. It is of utmost importance to be sure there is no intra-arterial injection of contrast. Although this location of needle placement usually will not contain a radicular or a vertebral artery, these arteries can be atypically located. In case of an intra-arterial injection, the contrast will move and disappear during live fluoroscopy. If this is the case, one can redirect the needle until contrast is not seen entering an artery. If contrast injection leads to rapid dilution of the contrast material, it may imply that there has been subarachnoid needle placement. In this case, abort the procedure and give enough time for the puncture to heal as injection even into another location may lead to entrance of medication into the subarachnoid space through the puncture hole created. Once it has been confirmed by AP and oblique views that there has been correct needle placement, contrast injection has been negative for intra-arterial and subarachnoid injection, the contrast appropriately outlines the spinal nerve, and injection of contrast is negative for pain or paraesthesia, the local anaesthetic and steroid (3–5 cm^3 of mixture containing 4 mg dexamethasone) can be given. Once the medication has

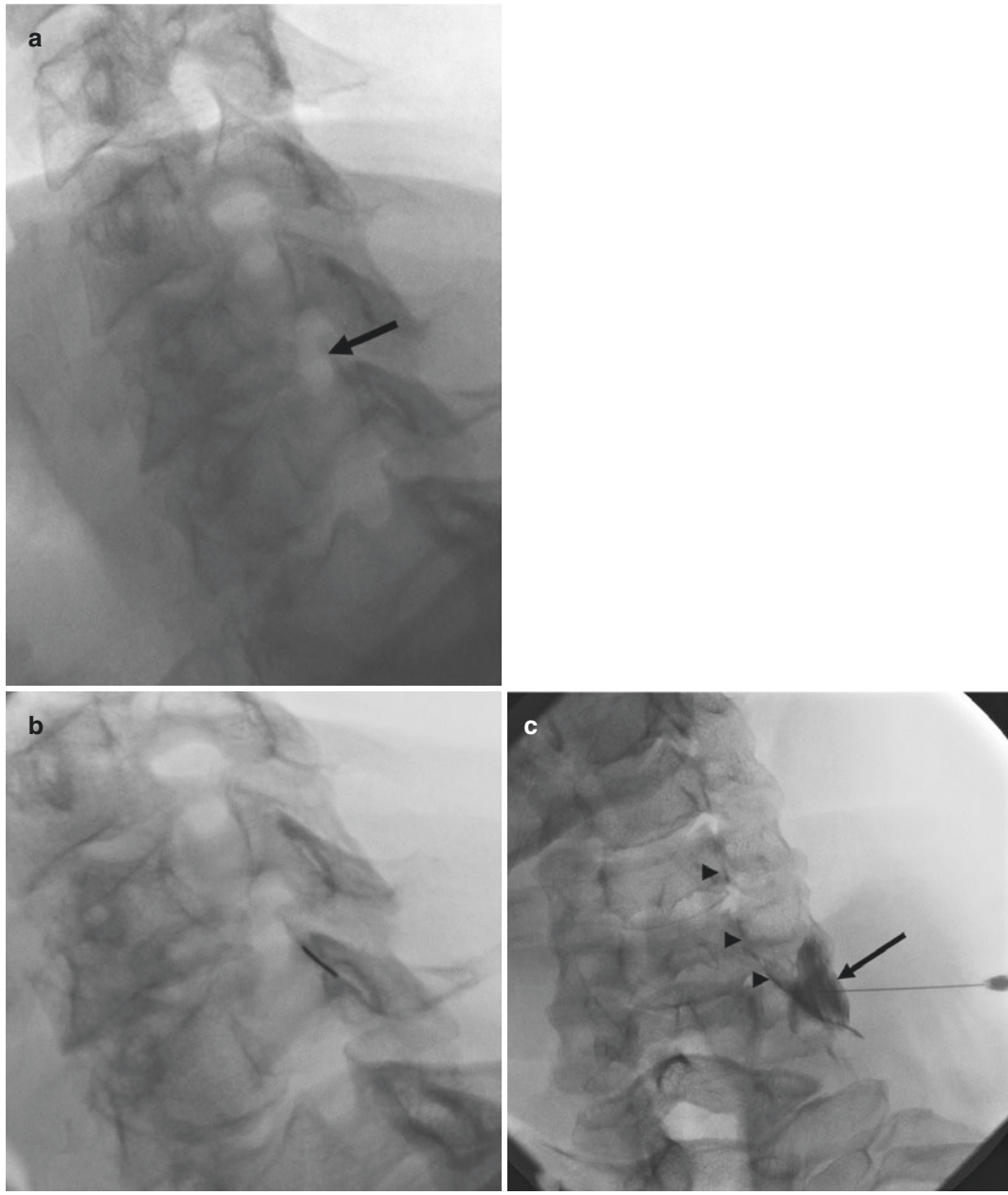

Fig. 1 (**a**) Ipsilateral oblique view demonstrating posterior portion of cervical neural foramen (arrow). (**b**) 25G needle directed toward posterior margin of cervical neural foramen. (**c**) AP view demonstrating cervical foraminal filling

been injected, the needle is removed with a saline or local anaesthetic flush to clear the needle and track of steroid. The area that was prepped should be cleansed and a bandage placed over site of needle insertion. The patient should then be taken to a recovery area where they should be monitored for complications resulting from conscious sedation as well as complications from the procedure itself.

3.4 Cervical Interlaminar Epidural

3.4.1 Injection Technique

This procedure can be performed by either a loss of resistance technique or a hanging drop technique. One technique has not been shown to be better than the other; thus, the choice of technique is based on physician preference.

3.4.2 Loss of Resistance Technique

The cervical interlaminar technique can be performed in either a sitting, lateral, or prone position. Each position has its own advantages and disadvantages. Since most pain practitioners use fluoroscopy to perform cervical epidural injections, the prone or lateral position is utilized. The cervical spine should be flexed to maximize the opening of the intervertebral spaces.

Once the patient is appropriately positioned, the neck is prepped and draped in a sterile manner, and AP fluoroscopy is used to identify the interspace that will be entered. A 17- or 18-gauge Tuohy needle (3.5 in.) is suitable for most patients. The lamina of the inferior vertebra (i.e. the lamina of C6 if performing a C5-C6 injection) is noted on AP fluoroscopy (Fig. 2a). The skin and subcutaneous tissues overlying the area

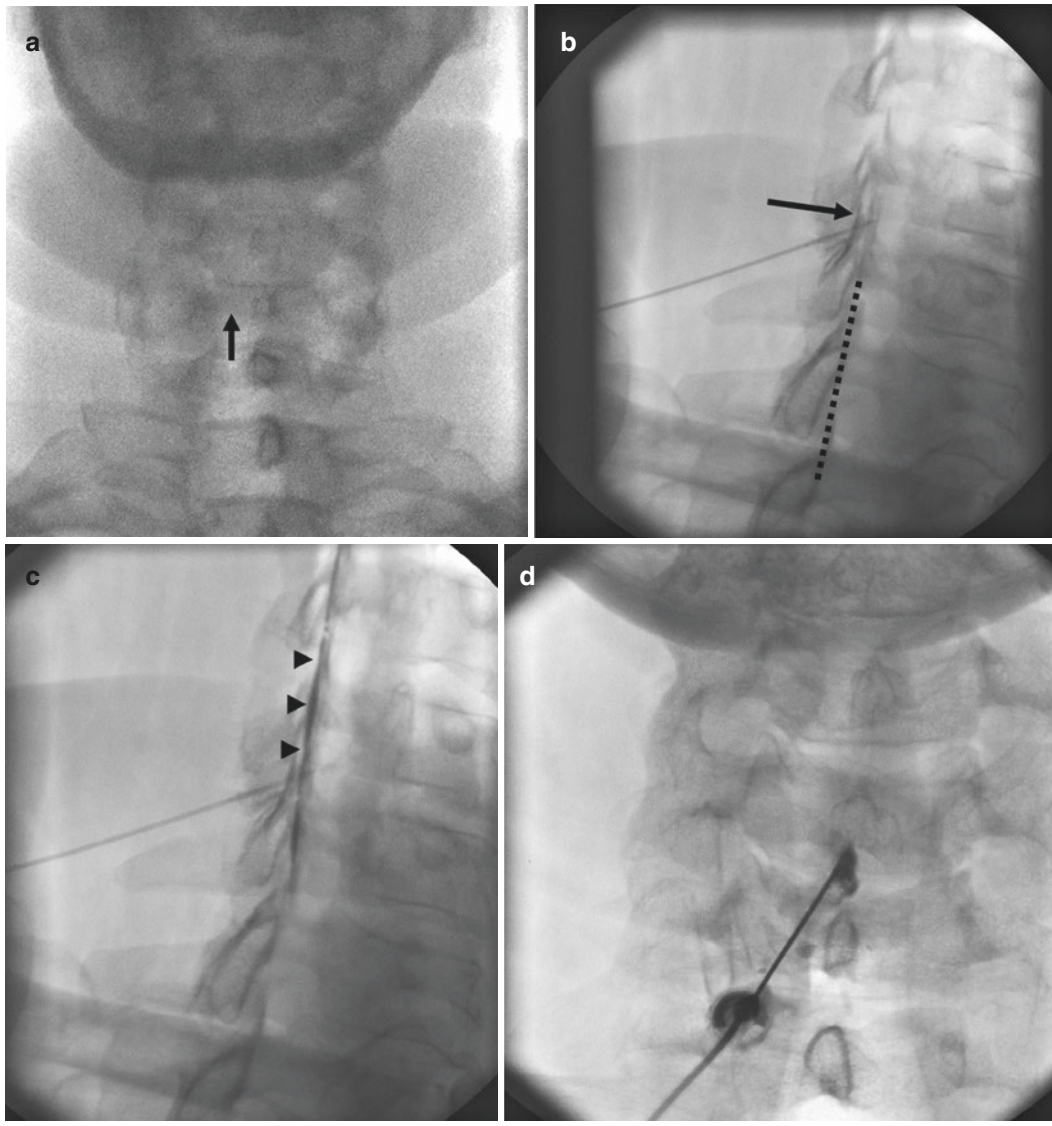

Fig. 2 (**a**) PA view for C5-6 midline cervical epidural injection (arrow). (**b**) Forty-five degree contralateral oblique showing the shingled appearance to the lamina and the needle tip position near the spinal canal (arrow). The dotted line marks the inner cortex of lamina (**c**) Contrast confirms epidural location (arrowheads). (**d**) PA view shows needle directed toward midline

are then anaesthetized with 1% lidocaine. The epidural needle is then slowly advanced under intermittent fluoroscopy until contact is made with the lamina. The depth of the needle should be noted. Once the lamina has been contacted, the stylet is removed, and a syringe is connected to the needle. The syringe can be filled with air, sterile saline, or both to check for loss of resistance. The needle is then walked off the lamina and into the epidural space. This should be performed using a two-handed technique with the handholding the needle stabilized against the patient's neck to protect against needle movement if the patient moves. The syringe is slowly advanced while always maintaining continuous pressure against the plunger. Contralateral oblique tilt is utilized to view laminae and spinal canal guiding the depth of needle insertion (Fig. 2b, c). Once the bevel passes into the epidural space, there is a sudden loss of resistance. The syringe is then removed from the needle, and 1 mL of contrast is injected. Epidural spread of the contrast should be noted (Fig. 2d). If subarachnoid spread (dilution) is noted, the procedure should be aborted as the puncture site may act as a gateway for local anaesthetic and steroid to enter the subarachnoid space even if the injection is attempted in another intervertebral space. Once needle location in the epidural space is confirmed, negative aspiration for blood and cerebrospinal fluid (CSF) must be confirmed; then, the medication can be injected. The needle is then withdrawn with a local anaesthetic or saline flush to remove steroid from the needle and injection track. The spread of medication in the epidural space is dependent on volume of injectate, dilation of the veins, anatomic differences in the epidural space, and age and height (Waldman 2007b). A number of local anaesthetics can be used including lidocaine and bupivacaine. Generally, about 7 mL (8–12 mg dexamethasone) is enough volume to adequately cover the nerve roots with local anaesthetic and steroid (Cronen and Waldman 1990).

3.4.3 Hanging Drop Technique

The hanging drop technique is an alternative to the loss of resistance technique to signify entrance into the epidural space. The technique is similar to the loss of resistance technique initially as the Tuohy needle is advanced until lamina is contacted. At this point, instead of attaching a glass/plastic loss of resistance syringe, the needle is filled with saline until a bubble of fluid is visible at the hub. The needle is slowly advanced, and once the needle enters and passes through the ligamentum flavum, the drop of fluid is drawn in. This is thought to be due to the pressure in the epidural space being lower than atmospheric pressure. A lateral fluoroscopic view can be used to confirm proper positioning of the needle tip in the epidural space. The remainder of the procedure is similar to that described for a loss of resistance technique.

3.5 Complications

3.5.1 Drug Related

Corticosteroids: mostly due to systemic absorption and are short-lived. It includes rash, nausea, pruritis, transient rise in blood pressure and blood glucose. More severe reactions include a Cushingoid response and adrenocortical failure. Local anaesthetics: rash, nausea, and accidental intrathecal injection with resultant spinal anaesthesia. Systemic absorption can lead to seizures and refractory cardiac arrhythmias.

3.5.2 Procedure Related

Complications can be associated with both routes of access. These include postdural puncture headaches, infection, development of epidural hematoma (which could lead to quadriplegia), subarachnoid injection leading to a complete spinal block, and direct cervical spinal cord trauma. However, the incidences of these complications are lower in interlaminar injections if the procedure is carried out in a cooperative patient using fluoroscopy and contrast medium (Abbasi et al. 2007). Multiple case reports of serious complications have been reported after cervical transforaminal injections, ranging from paraplegia to death. This is thought to be due to accidental injection of particulate steroid into a cervical radicular artery. This may lead to spinal cord infarction followed by impairment. Given the positive results seen with the interlaminar

approach and the serious complications associated with the transforaminal approach, it may be prudent to consider the former rather than the latter.

4 Lumbar Epidural Injections

Given the high prevalence of back pain and radiculopathy, placing corticosteroid and local anaesthetic into the lumbar epidural space is one of the most common procedures performed for chronic pain management. A systematic review by Parr et al. (Parr et al. 2009) found positive correlations between short-term pain relief of disk herniation and radiculitis with epidural corticosteroids. Evidence is lacking for long-term relief as well as short- and long-term relief of pain due to spinal stenosis and discogenic pain without radiculitis.

4.1 Indications

Common indications for lumbar epidural injections are:

- Lumbar radiculopathy
- Lumbar degenerative disk disease
- Lumbar disk herniation
- Lumbar spinal stenosis
- Lumbar postlaminectomy (failed back) surgery syndrome
- Lumbar vertebral compression fractures
- Postherpetic neuralgia/herpes zoster
- Cancer-related pain

4.2 Contraindications

Similar to as mentioned in Cervical Epidural Injection section.

4.3 Lumbar Transforaminal Epidural

4.3.1 Injection Technique

After discussing the risks and benefits and obtaining written informed consent, the patient is taken to the fluoroscopy suite and placed in a prone position. The area of the lumbar spine is then prepped and draped in a sterile manner. AP fluoroscopy is used to identify the level to be injected with cranio-caudal tilt to flatten the vertebral end plate. An oblique view is then obtained toward the side that will be injected. This is done until the superior articular process of the inferior level is in line with the 6 o'clock position of the pedicle of the superior level (Fig. 3a). The entry point is marked and the skin and subcutaneous tissues overlying the area are anaesthetized with 1% lidocaine. Using intermittent fluoroscopy, the needle is guided to the target point in small increments. The area in which it is appropriate to place the needle has the following boundaries on AP view: the upper border is a line that runs under the pedicle at the 6 o'clock position, the lateral boundary is a sagittal line that runs caudad from the lateral aspect of the pedicle to the segmental nerve, and the hypotenuse of this triangle connects the two lines and runs parallel to the lateral border of the nerve (Raj et al. 2008). It is in this area where there is the least chance of hitting a segmental nerve or a vascular structure. Once the caudal aspect of the pedicle at the 6 o'clock position is encountered, the needle tip is turned caudad until it slips off the pedicle and into the neural foramen (Fig. 3a, b). Using a needle with the tip bent away from the bevel can make this step of the procedure easier to accomplish. Lateral fluoroscopy is then used to confirm that the needle is in the neural foramen (Fig. 3e). Occasionally, if the needle is placed too deep, the patient may experience a paraesthesia due to accidental touching of the segmental nerve. The needle should be withdrawn and the paraesthesia allowed to resolve. Once the needle is in the correct location, both AP and lateral fluoroscopy should be used to verify its position prior to injection. The AP view should show the needle just inferior to the 6 o'clock position of the superior level's pedicle (Fig. 3c, d). Lateral fluoroscopy should show the needle tip in the foramen below the pedicle and in the middle portion of the foramen. Once the needle position is confirmed and negative aspiration for blood or CSF has been observed, 1 mL of contrast is injected during live fluoroscopy in an AP view (Fig. 3f). The contrast

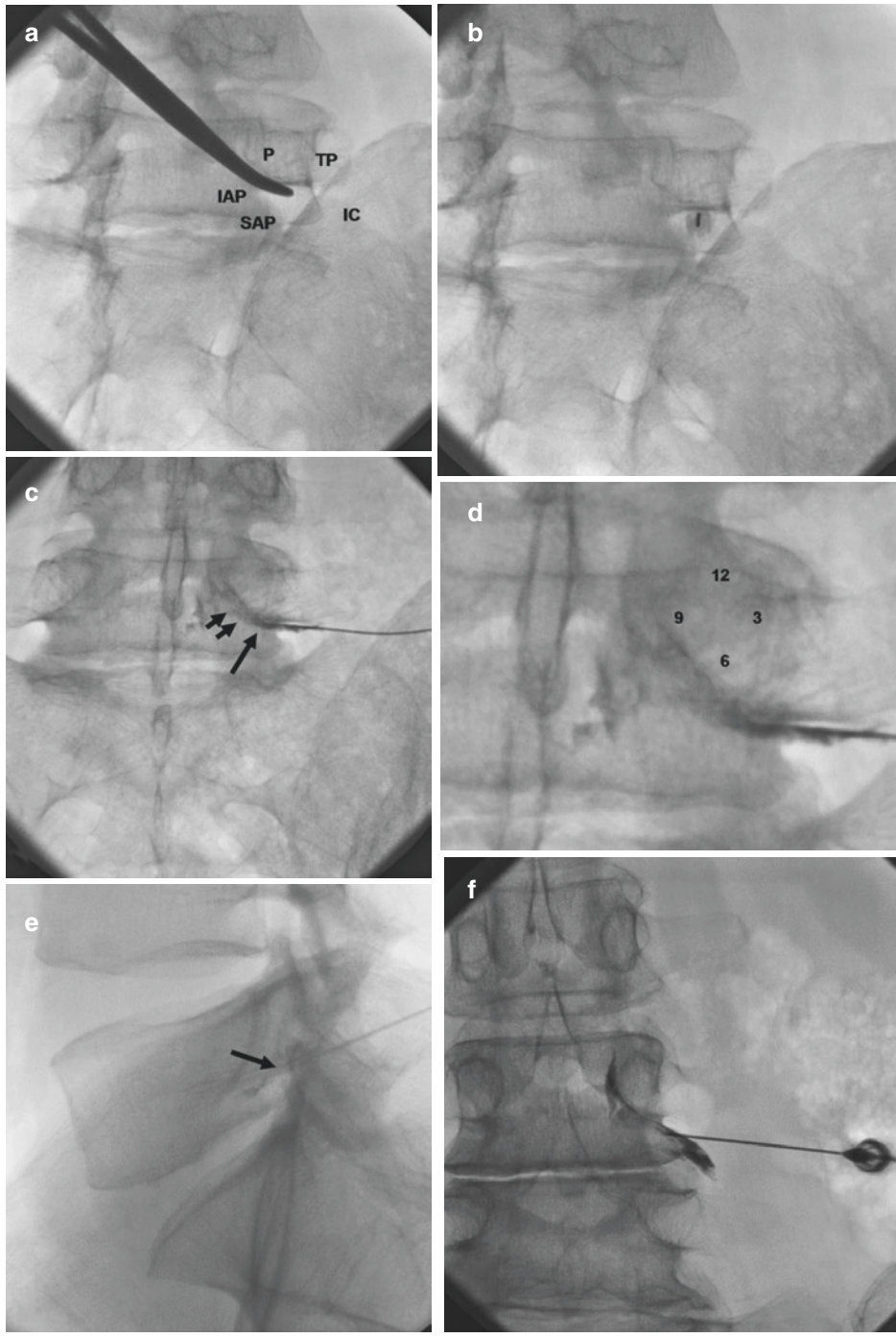

Fig. 3 Right L5 Transforminal epidural steroid injection (TFESI). (**a**) Target marked with forceps. P–L5 pedicle; TP–L5 transverse process; IAP–L5 inferior articulating process; SAP–S1 superior articulating process; IC iliac crest. (**b**) Bull's-eye needle placement at the 6 o'clock position of the pedicle. (**c**, **d**) AP fluoroscopic image showing proper needle tip position (long arrow). Contrast should flow under the pedicle into the epidural space (short arrows). (**e**) Lateral fluoroscopic image showing needle tip placement within the superior aspect of the neural foramen. (**f**) Right L4/L5 TFESI AP fluoroscopic image in a different patient with proper 50/50 contrast flow pattern

should be seen outlining the nerve root and flowing into the epidural space. The medication usually 2–3 mL local anaesthetic and steroid mixture (40 mg triamcinolone or 10 mg dexamethasone) can now be injected. The needle is removed with a local anaesthetic or saline flush to clear the needle and injection track of steroid. The area that was prepped should be cleansed and a bandage placed over site of needle insertion. The patient should then be taken to a recovery area where they should be monitored for complications resulting from conscious sedation as well as complications from the procedure itself.

4.4 Lumbar Interlaminar Epidural

4.4.1 Injection Technique

After discussing the risks and benefits and obtaining written informed consent, the patient is taken to the fluoroscopy suite and placed in a prone position. A pillow or cushion can be placed under the abdomen to decrease lumbar lordosis and open up the intervertebral space. The area of the lumbar spine is then prepped and draped in a sterile manner. AP fluoroscopy is used to locate the target entry level (Fig. 4a). Cranial/caudal tilting can be done until the interspace is optimally visualized. Once the site is chosen and the area is anaesthetized, the needle is placed toward the side that the patient has pain. A 17- or 18-gauge Tuohy needle is directed under fluoroscopic guidance until the inferior lamina of the entry level is contacted. A loss of resistance syringe is then attached. The needle is then angled cephalad, and a two-handed technique is used to stabilize the needle and advance it slowly toward the epidural space. The loss of resistance technique can be done with continuous pressure on the syringe until there is loss of resistance. Once there is loss of resistance, lateral fluoroscopy can be utilized to confirm location of the needle tip in the epidural space (Fig. 4b). A false loss of resistance can occur in the subcutaneous tissue. It is also possible that a loss of resistance may not occur until the needle is in the subdural or subarachnoid space. After confirming accurate needle placement, negative aspiration should be confirmed for blood and CSF, and 1–2 mL of contrast is then injected to visualize epidural spread (Fig. 4c, d). The contrast should have a smooth flow during injection. Once appropriate spread of contrast is confirmed, the medication (40–80 mg triamcinolone) can be injected. Caution must be exercised to avoid intraneural injection which would cause immediate and severe pain. If severe pain occurs on injection, the needle should be repositioned.

4.5 Complications

4.5.1 Drug Related

Similar to as mentioned in Cervical Epidural Injection section.

4.5.2 Procedure Related

Procedural complications include postdural puncture headache (from accidental dural puncture and CSF leak), vasovagal reaction, subdural infiltration, neural injury, and permanent injury to the spinal cord (if in the upper lumbar levels). Permanent spinal cord injury can be secondary to either direct needle trauma or disruption of blood supply to the spinal cord. The artery of Adamkiewicz is a major artery that supplies the lumbar region of the spinal cord. It enters the spinal canal in 80% of people between T8 and L3 on the left (Waldman 2007c). Injury can be avoided by making sure the needle is not too lateral in the neural foramen on AP fluoroscopy (Waldman 2007c). Other complications associated with procedure are rare, but many case reports have been written. These include infectious processes like meningitis, abscess, and an epidural hematoma (a surgical emergency).

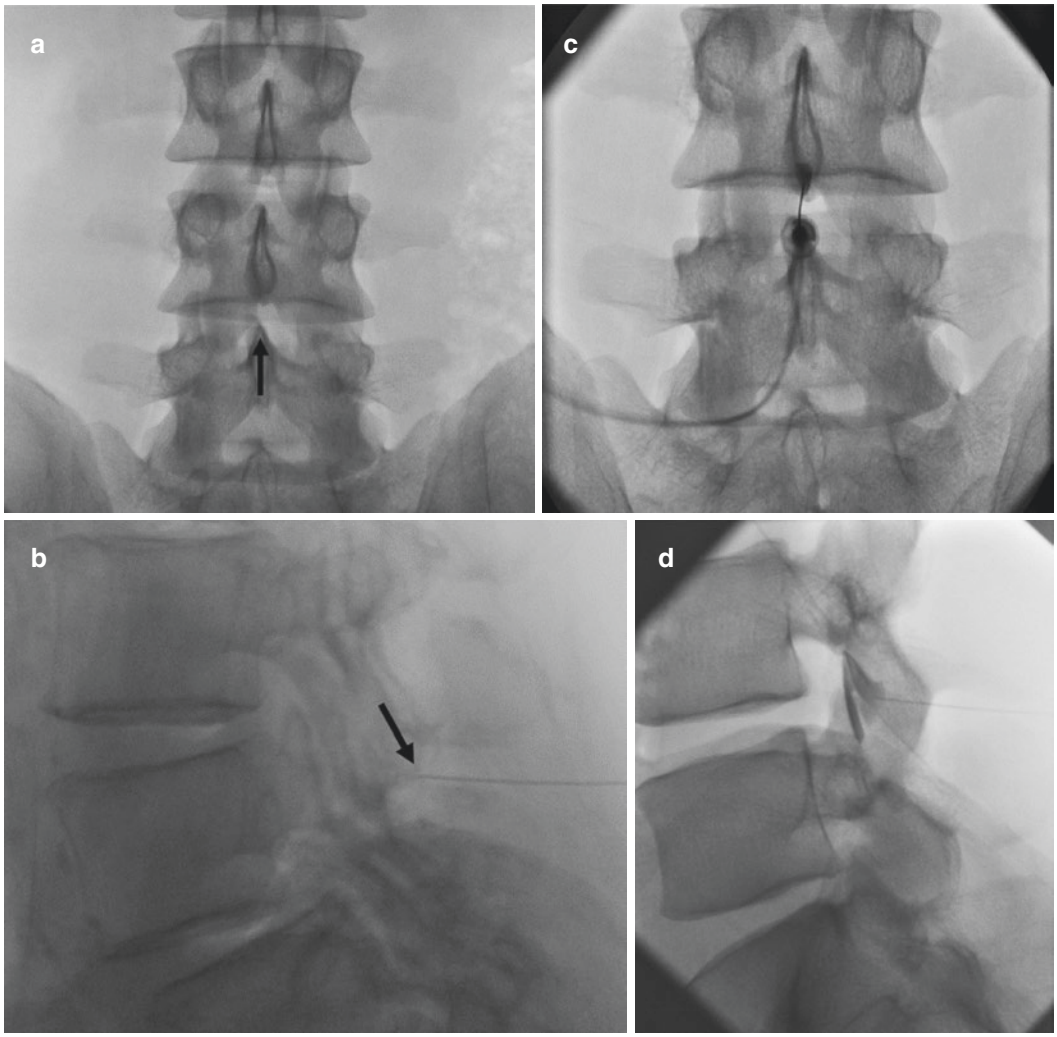

Fig. 4 Midline interlaminar epidural steroid injection. (**a**) Scout AP fluoro spot image showing the skin entry site for planned L4/L5 interlaminar space (arrow). (**b**) Lateral fluoro spot image showing target site for needle tip placement 1–2 mm deep to the dorsal margin of the inferior articulating process. This usually places the needle tip in the ligamentum flavum (arrow). (**c**) AP fluoro spot image following injection of a small amount of contrast. The contrast pools around the tip of the needle. (**d**) Lateral fluoro spot image showing contrast pooling along the dorsal epidural space

5 Caudal Epidural Injection

The caudal approach to the epidural space was performed years prior to the lumbar approaches.

5.1 Indications

One of the primary uses for the caudal approach to the epidural space is in patients who have had lumbar surgery which could make lumbar approaches more difficult or even impossible. Severe degenerative changes may also warrant a caudal approach.

Other indications are:

- Sacral/coccygeal neuralgia
- Interstitial neuritis
- Pelvic pain
- Penile/Testicular pain

5.2 Contraindications

Similar to as mentioned in Cervical Epidural Injection section.

5.3 Caudal Epidural Injection Technique

After discussing risks and benefits, answering questions, and obtaining written informed consent, the patient is brought into the procedure room and placed in a prone position. A cushion can be placed under the lower abdomen which will decrease lumbar lordosis and help decrease the angle of the sacral hiatus. The skin overlying the lower lumbar and gluteal region is prepped and draped in a sterile manner.

Lateral fluoroscopy can be used to identify the sacral hiatus. Manual palpation can also be used to identify the sacral cornu at the entrance to the sacral hiatus. Once the sacral hiatus has been identified, the skin and subcutaneous tissues can be anaesthetized. A 22- or 25-gauge needle can be used to enter the sacral canal. It does not need to be longer than 1.5 in. A 17- or 18-gauge Tuohy needle can be used if the plan is to thread a catheter to the lumbar region for more targeted block. The needle is then inserted at a 45° angle until a "pop" is felt which signify passage through the sacrococcygeal ligament and then angled caudal to avoid contact with the bone inside the sacral canal. The needle is then advanced about 1 cm, negative aspiration for blood is confirmed, and contrast can be injected to confirm placement of the needle in the canal (Fig. 5a, b). If there is resistance to injection of air or contrast, the needle can be rotated as the bevel may be against the bony wall of the sacral canal. Once the needle is correctly placed, either a medication (10 mL containing 40–80 mg triamcinolone) can be directly injected or a catheter can be placed and advanced to a higher level for a more targeted injection. If a catheter is used, less volume can be used as the medication is deposited near the nerve roots, causing pain. Once the medication has been injected, the needle is removed with a saline or local anaesthetic flush to clear the needle and track of steroid. The area that was prepped should be cleansed and a bandage placed over site of

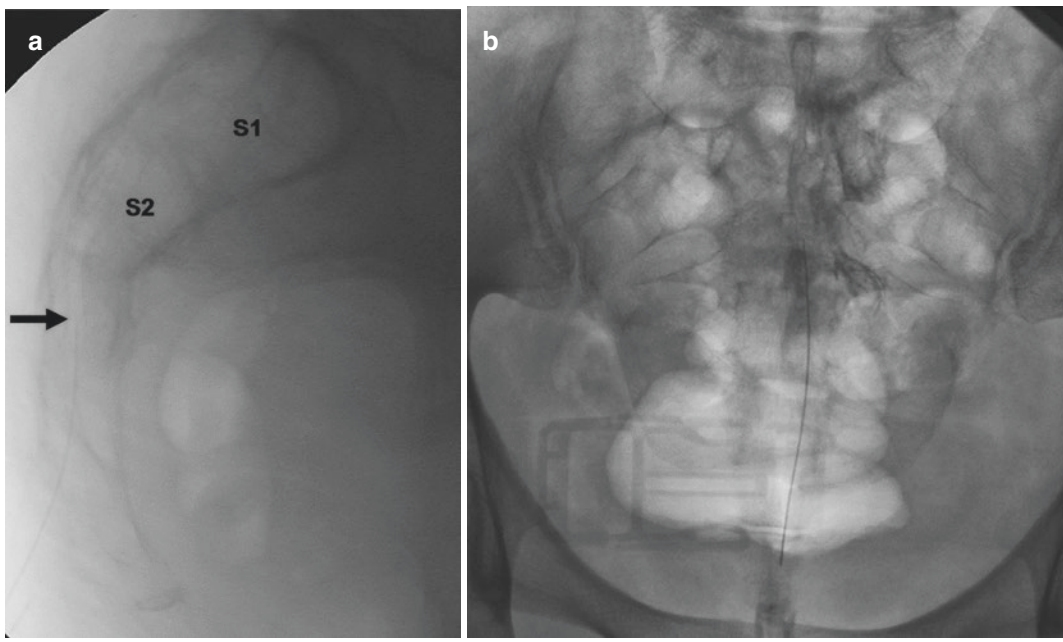

Fig. 5 (**a**) Lateral projection showing proper needle tip position at the mid to superior portion of the S3 vertebral body. (**b**) "Christmas tree" appearance of contrast distribution in a caudal injection

needle insertion. The patient should then be taken to a recovery area where they should be monitored for complications resulting from conscious sedation as well as complications from the procedure itself.

5.4 Complications

5.4.1 Drug Related

Similar to as mentioned in Cervical Epidural Injection section.

5.4.2 Procedure Related

Procedural complications include postdural puncture headache (from accidental dural puncture and CSF leak), vasovagal reaction, subdural infiltration, and neural injury. Infection, although rare, can be a higher risk with this approach given the needles entry site closer to the anus when compared to lumbar approaches. This is very important consideration especially in immunocompromised patients.

6 Conclusion

Indications and contraindications must be carefully reviewed prior to performing epidural steroid injections in the cervical and lumbar regions. There are many ways with own benefits and risks to access the epidural space. Fluoroscopy is helpful in correct placement of needle however facilities must always be available to deal with catastrophic complications.

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Spinal Facet Injections for Palliative Pain Management

Will Guest and Manraj Heran

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Abstract

The facet joints are paired synovial joints of the posterior elements of the spinal column. They contribute to stabilization of the spine and transmission of axial loads, while enabling flexion/extension and rotational motion. The facet joints are a frequent source of pain in the adult population, related to degenerative, neoplastic, rheumatologic, infectious, and traumatic processes. Some of these processes, such as pathologic fractures or opportunistic infection, may occur with greater frequency among patients receiving palliative care. The anatomy of the facet joint is reviewed,

W. Guest · M. Heran (✉)
Division of Neuroradiology,
Department of Radiology, University of British Columbia, Vancouver, BC, Canada
e-mail: will.guest@vch.ca; manraj.heran@vch.ca

© Springer Nature Switzerland AG 2021

P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_11

followed by a discussion of the causes of facet pain and the treatment options available to provide short- and long-term relief, including facet injections, median branch blocks, and radiofrequency ablation.

1 Introduction

The facet (or zygapophyseal) joints are paired synovial joints of the posterior elements of the spinal column, involving every intervertebral level from C2-3 to L5-S1. They contribute to stabilization of the spine and transmission of axial loads, while enabling flexion/extension and rotational motion. The facet joints are a frequent source of pain in the adult population, related to several pathologic processes. Some of these processes, such as fractures or opportunistic infection, may occur with greater frequency among patients receiving palliative care. In this chapter, the anatomy of the facet joint will be reviewed, followed by discussion of the causes of facet pain and the treatment options available to provide short- and long-term relief.

2 Anatomy and Function of the Facet Joints

The bilateral facet joints function together with the intervertebral disc to balance the need for stability and mobility in spine biomechanics. The facet joint itself is composed of subchondral bone covered by articular cartilage, surrounded by a synovium and fibrous capsule. The orientation of the facet joint in the transverse and sagittal planes, and the curvature of the joint line, varies between the cervical, thoracic, and lumbar spine to reflect the varying requirements for flexibility and load-bearing at different levels of the spinal column. The surface area of the facet joints increases at lower levels to distribute greater axial loads (O'Leary et al. 2018).

Although the articular cartilage of the facet joint is not innervated, there is a rich nerve supply to the subchondral bone, synovium, and joint capsule of the facet. Innervation is principally from the medial branch of the nerve root dorsal ramus, which is involved in both pain sensation and proprioception. The medial branch therefore becomes a target for pain interventions as described below. Innervation of the facet comes from the nerve roots above and below the joint.

3 Disease Processes Affecting the Facet Joints

Spinal pain is a common cause of disability, with approximately 29% of American adults experiencing back pain and 15% experiencing neck pain. The facet joints are estimated to be responsible for 16–40% of low back pain and 39–67% of pain in the neck (O'Leary et al. 2018). The population of patients receiving palliative care have risk factors for several causes of facet pain: weakened bone due to metastatic disease or treatment effects increases risk of fracture, immunosuppression from chemotherapy, or lymphoproliferative disease increases the risk for septic arthritis, and the advanced age of some palliative patients increases the likelihood of symptomatic degenerative facet arthropathy.

Facet joint pain frequently has a nonspecific clinical presentation, including unilateral or bilateral back pain radiating to the buttocks, groin, or thigh, but stopping above the knee. Patients also tend to have back or neck stiffness, worst in the mornings, as well as discomfort which can be exacerbated on hyperextension. However, only in about 15% of cases can an etiology of back pain be diagnosed on clinical examination alone (Perolat et al. 2018). Noninvasive imaging with CT or MRI is therefore important to investigate sources of back pain and identify a facet joint as a probable cause. CT more clearly defines bony anatomy, including the presence of periarticular osteophytes or fractures. MRI better shows surrounding soft tissue or bone marrow edema, as well as joint effusions and mass effect on neural elements. Metabolic imaging, especially single photon emission CT (SPECT/CT) with a radiotracer sensitive to bone turnover such as ^{99m}Tc-MDP, can localize the

facet joints exhibiting the greatest scintigraphic activity (Russo et al. 2017) to identify targets for pain management injections.

3.1 Degenerative

Osteoarthritic changes at the facet joints are extremely common: a cadaveric study evaluating the presence of osteophytes at the lumbar facet joints found it is an essentially ubiquitous finding in adults over the age of 60 years (Eubanks et al. 2007). As with other joints, the typical findings include joint space narrowing from cartilage loss, periarticular osteophytes, subchondral cysts, and hypertrophy of the articular processes (Fig. 1). In the lumbar spine, facet arthropathy is typically worst at L4-5 and L5-S1 (Eubanks et al. 2007), whereas in the cervical spine it occurs most often at C2-3, C3-4, and C4-5 (Park et al. 2014). Given this ubiquitous finding, it can sometimes be challenging to determine of an individual's back or neck pain is on the basis of facet degenerative changes.

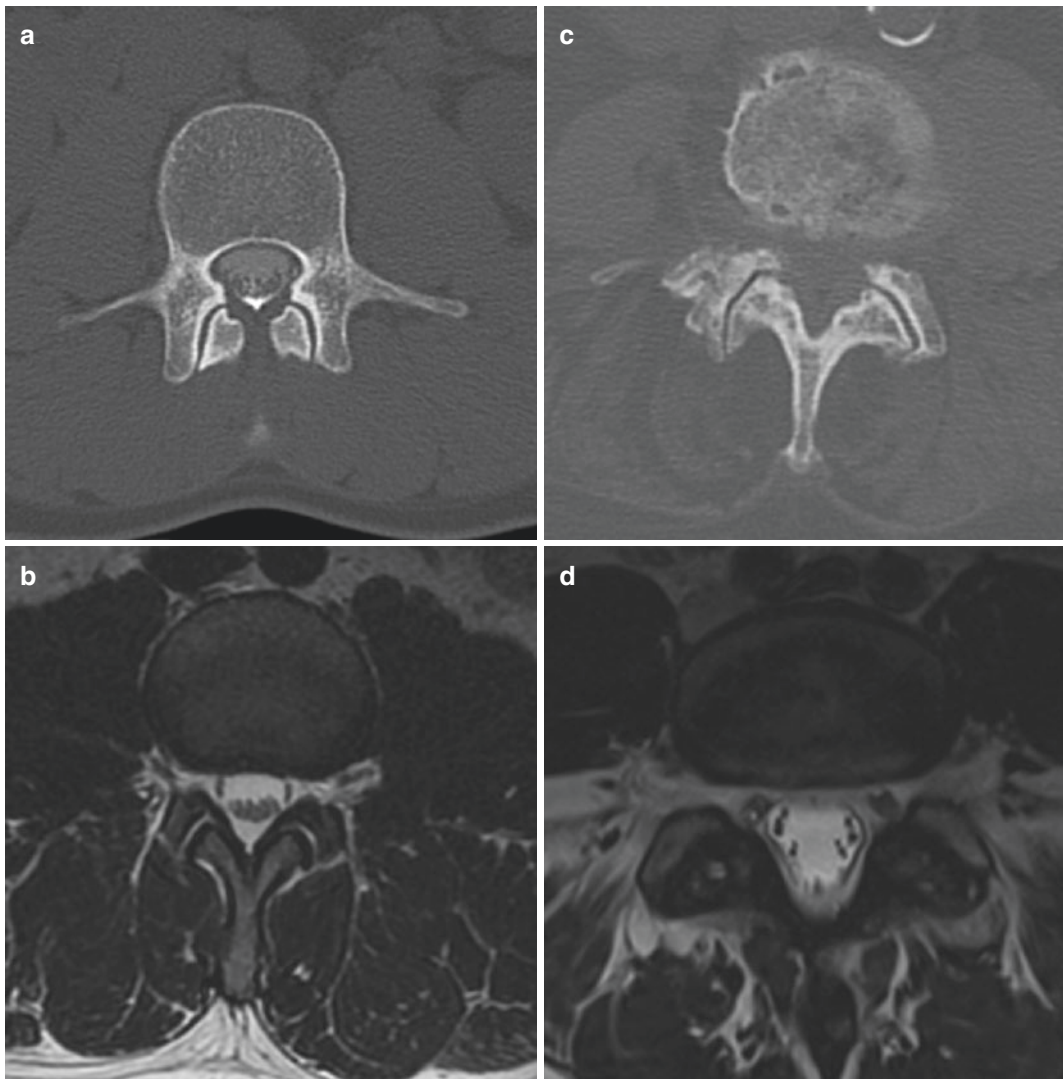

Fig. 1 Normal lumbar facet joints on CT (**a**) and T2-weighted MRI (**b**). Advanced lumbar facet arthropathy on CT (**c**) and MRI (**d**). Note the joint space loss, periarticular sclerosis, marginal osteophytes, and subchondral cysts

A particular problem of facet joint degeneration is that the resulting hypertrophy of the joint or associated synovial cyst formation can contribute to narrowing of the spinal canal, subarticular recesses, and neural foramina, with mass effect on exiting or traversing nerve roots in the spinal canal.

3.2 Neoplastic

Patients with advanced malignancy may have bony metastatic disease adjacent to or involving the facet joints (Fig. 2). Metastatic lesions can encroach on the joint capsule, causing irritation with movement; furthermore, weakening of adjacent bone may predispose to pathologic fracture. Benign neoplasms of the spinal posterior elements, including aneurysmal bone cysts, osteoblastomas, and osteoid osteomas, may produce similar effects by involvement of the facets, or by altering the local biomechanics, with potential acceleration of facet degenerative disease.

Treatments for solid and hematologic malignancy, including radiotherapy and corticosteroids, may lead to loss of bone mineral density and/or osteonecrosis, creating a risk for insufficiency fractures that, while typically involving the vertebral bodies, may also extend to the pedicles and facets.

3.3 Rheumatologic

As synovial joints, the facets can be affected by inflammatory arthropathies such as rheumatoid arthritis. Bony ankylosis of the cervical facets can be associated with cervical myelopathy and instability in a cohort of patients with rheumatoid arthritis going for spinal surgery (Iizuka et al. 2017). Lumbar endplate and facet erosion were detected in 70.6% and 76.6%, respectively, of rheumatoid arthritis patients by MRI (Yamada et al. 2014).

Ankylosing spondylitis may lead to slowly progressive fusion across the facet joints, with resulting loss of mobility and postural deformity. The greater rigidity of the spine also predisposes to unstable, three-column fractures with even minor trauma (Fig. 3).

3.4 Infectious

Septic facet arthritis presents with insidious onset of back pain that can rapidly progress to a

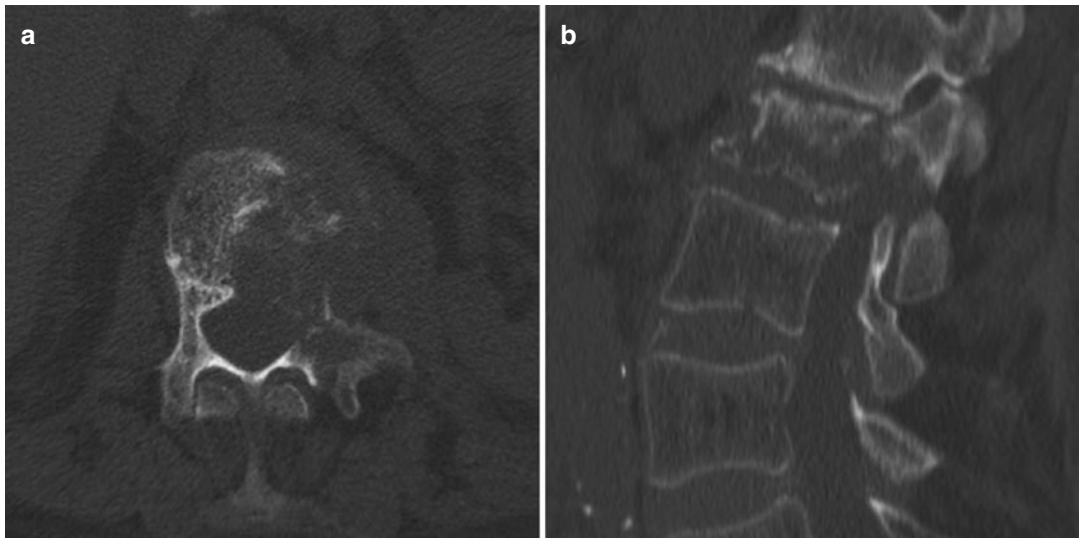

Fig. 2 Metastatic encroachment on the facet joint on axial (**a**) and sagittal (**b**) CT images. The patient had a sarcoma metastatic to the L2 vertebral body, which extended posteriorly into the pedicle and transverse process, abutting the left L2/3 facet joint

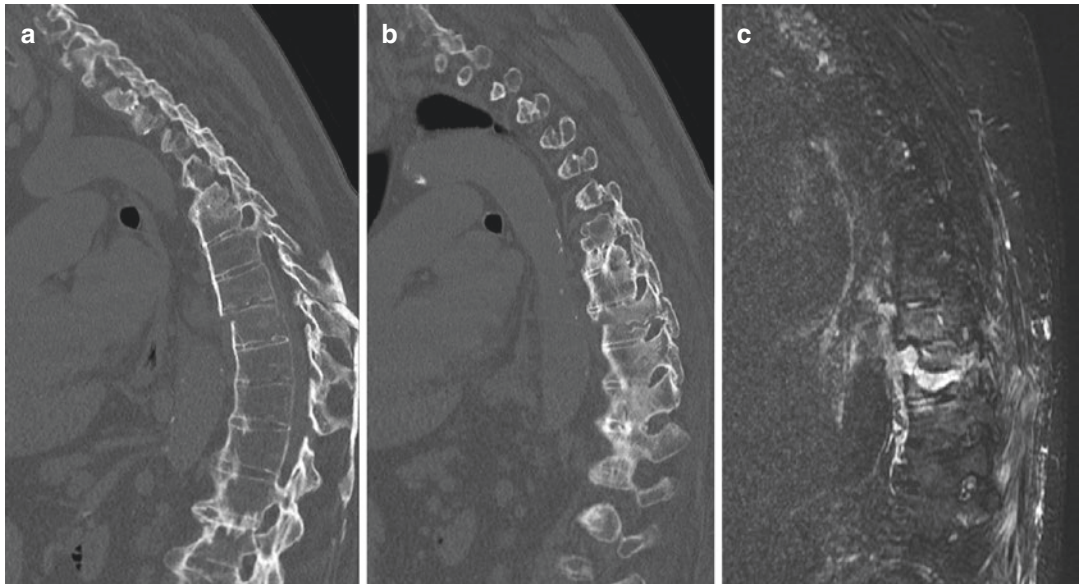

Fig. 3 Patient with advanced ankylosing spondylitis and unstable three-column mid thoracic fracture after a fall from standing height. (**a**) Mid-sagittal CT showing disruption of the bridging syndesmophytes at the anterior vertebral body, with the fracture line extending to the posterior cortex and the fused spinous processes. (**b**) Left parasagittal CT showing the fracture line extending to the neural foramen and into the left facet joint. (**c**) STIR MRI showing fluid in the fracture cleft extending to the facet joint with extensive surrounding edema

surgical emergency without prompt treatment. Clinical markers of infection, including fever, elevated white blood cell count, and elevated CRP or ESR are typically present; however, these features may be absent in the immunosuppressed population (including those receiving chemotherapy or stem cell transplant). This population is also at increased risk of infection. MRI is the preferred initial modality for investigation, showing enhancement centered at the facet joint, with surrounding soft tissue edema on STIR sequences and frequently a joint effusion that can be aspirated for culture and sensitivity (Fig. 4).

3.5 Traumatic

Facet fracture-dislocations can occur with high-energy trauma, most commonly in the cervical spine. More relevant in the palliative care setting are pathologic or insufficiency fractures that can involve the facets, as described above.

4 Treatment Strategies for Facet Pain

As is generally true of pain management, a graded approach to treatment of facet-mediated pain should be used, starting with conservative measures, and progressing from less invasive to more invasive procedures. In a palliative care context, priority needs to be given to immediate pain relief and improvement of quality of life in the short to intermediate term.

Standard procedures and precautions should apply when performing all the interventions described below, including obtaining informed, written consent before the procedure, performing a time-out to confirm the side and level(s) to be treated, and using sterile technique. Guidelines for management of anticoagulants and antiplatelet agents around the time of the procedure vary with institution. Our local policy for facet injections or median branch blocks is to document an INR of 2 or lower and a platelet count of 20×10^9/L or higher for patients with risk factors

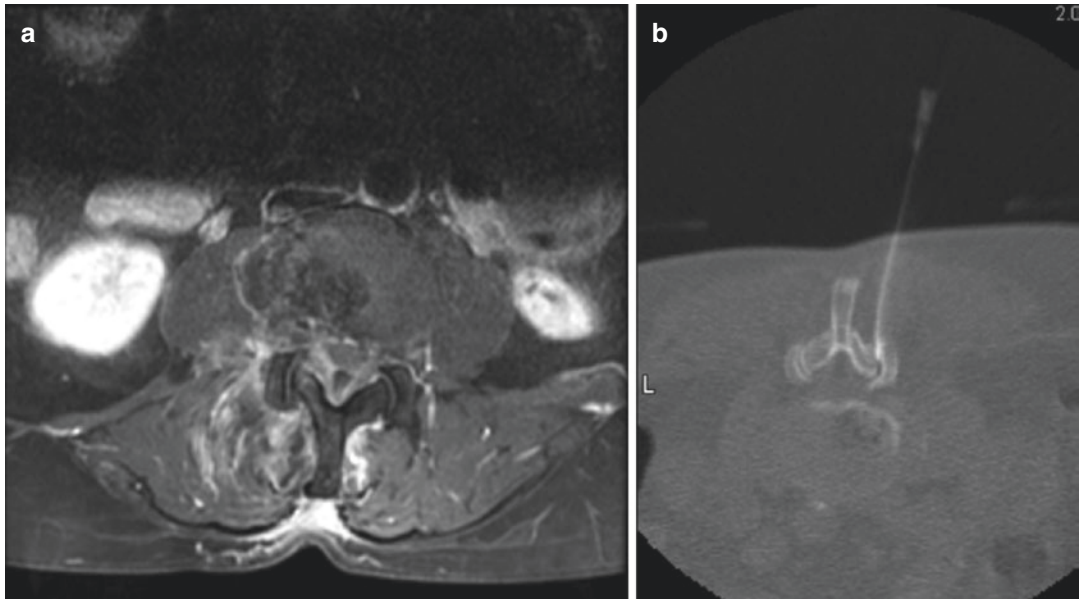

Fig. 4 (**a**) Post-contrast T1 fat sat MRI showing enhancement centered around the right L2/3 joint, suspicious for septic facet arthritis. (**b**) Aspiration of the facet joint was performed under CT guidance with a 22-gauge spinal needle, yielding purulent fluid

for liver disease or thrombocytopenia. Antiplatelet and anticoagulants generally do not need to be interrupted. For radiofrequency ablation, we require an INR of 1.5 or less and a platelet count of 50×10^9/L or higher; aspirin can be continued, but other antiplatelets and anticoagulants are usually held beforehand (the timing of stopping and restarting them around the time of the procedure varies depending on the medication and patient-related factors).

4.1 Conservative and Pharmacologic Therapies

With nonspecific low back pain and neck pain, imaging and clinical examination may fail to identify a focal anatomic cause. In the treatment of non-radicular chronic low back pain, exercise therapy, tai chi, yoga, acupuncture, and psychological therapies have been shown in randomized controlled trials or systematic reviews to provide small to moderate benefit (Barreto and Lin 2017). These approaches are also complementary to the more targeted treatments for facet pain described below. A stabilization exercise program was shown to augment the response to lumbar facet radiofrequency denervation, improving pain and physical performance (Cetin et al. 2019).

Nonsteroidal anti-inflammatory medications have a small effect on reducing facet-mediated pain, and the benefit was synergistic with corticosteroid facet injection (Sae-Jung and Jirarattanaphochai 2016). Although opioid medication for treatment of chronic back pain is generally discouraged, pain management in a chronic/palliative care setting presents a unique set of considerations, especially if there are multiple sources of pain or if the patient is too unwell for percutaneous interventions. Such treatment decisions should be managed by a specialist in palliative care or pain medicine.

4.2 Median Branch Blocks

Median branch blocks are a diagnostic test to confirm a facet joint as a source of pain. Each exiting medial branch of the dorsal ramus innervates the inferior aspect of the facet joint above

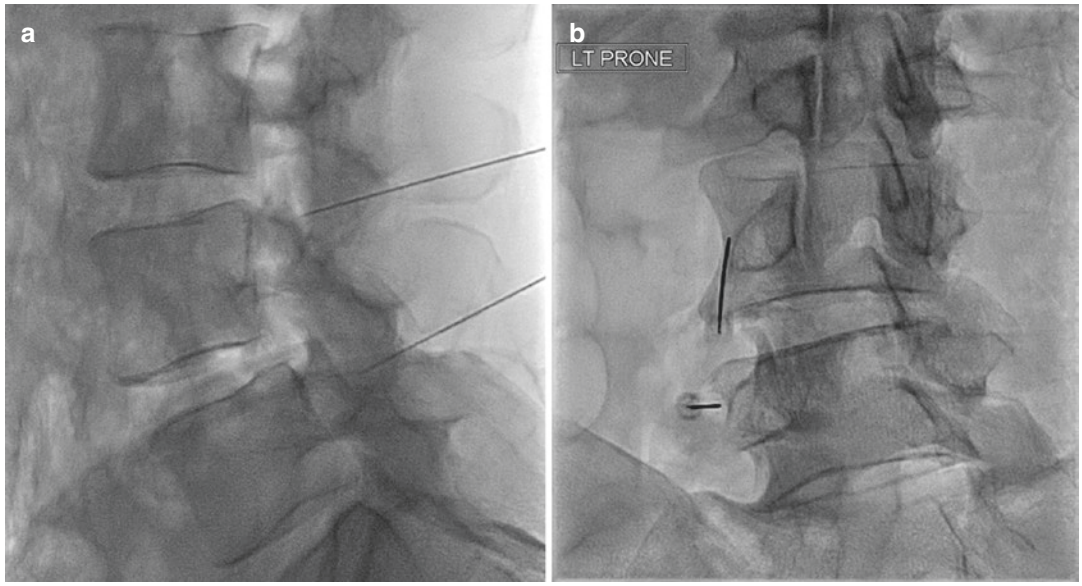

Fig. 5 Fluoroscopically guided median branch blocks of the left L3 and L4 nerve roots in the lateral (**a**) and left posterior oblique (LPO) projections (**b**)

and the superior aspect of the facet joint below. For this reason, it is important to perform blocks of the median branches above and below the targeted facet joint (e.g., if the L4-5 facet joint is being investigated, blocks of the median branches of the dorsal rami of the L3 and L4 nerve roots should be performed).

Median branch blocks are typically performed under fluoroscopic guidance, using a local anesthetic and recording a pain score before and after the procedure (Fig. 5). If the block is successful at eliminating the pain, this identifies the blocked facet joint as the source of pain. The patient is positioned prone on the fluoroscopy table, with the image intensifier angled obliquely to the side of the facet to be injected. After injecting local anesthetic in the skin and subcutaneous tissues with a 25-gauge needle, a 22-gauge spinal needle is advanced under intermittent fluoroscopy at the junction of the superior articular process of the facet and the transverse process of the vertebra (for thoracic and lumbar levels). Once bone is reached, the bevel of the needle is turned away from the neural foramen. Gentle aspiration on the spinal needle can be performed to ensure the needle tip is extravascular, and a small amount of myelography-safe iodinated contrast can also be injected to confirm safe needle positioning. Once satisfied that the needle is correctly positioned, 1 mL of long-acting local anesthetic is injected, with the needle removed and gentle pressure applied to the puncture site for hemostasis. Although median branch blocks are typically performed for diagnostic purposes, a corticosteroid can be mixed with the long-acting local anesthetic to perform a therapeutic block.

4.3 Radiofrequency Ablation

If the patient has pain relief from a diagnostic median branch block, then radiofrequency ablation can be performed to provide longer pain relief. Radiofrequency electrodes are navigated fluoroscopically into the region of the dorsal ramus medial branch (Fig. 6). Several different electrode placement techniques have been described, including oblique, posterolateral, and decline approaches (Gofeld and Faclier 2008). A small test current is applied to prove that the probe tip is optimally positioned on/immediately adjacent to the median branch. If the patient's pre-

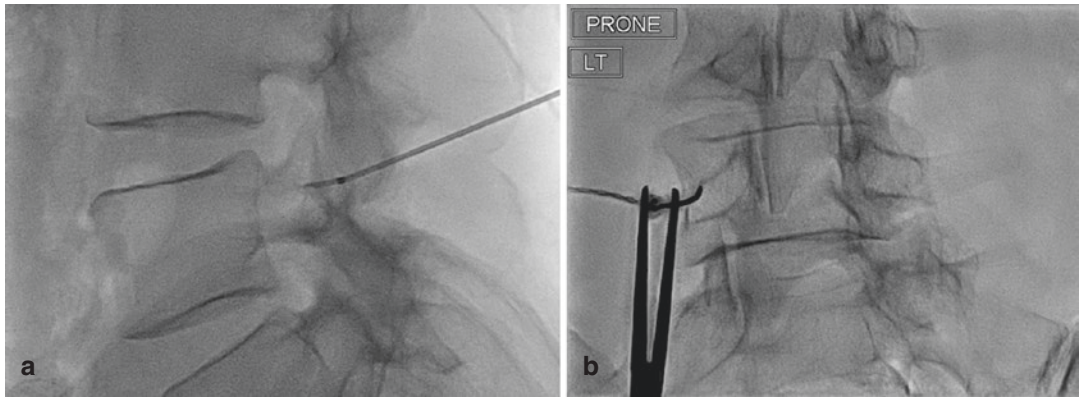

Fig. 6 Radiofrequency rhizotomy for left L4/5 facet-mediated pain, with the electrode shown in the lateral (**a**) and lateral posterior oblique (LPO) projections (**b**). The patient has transitional anatomy with a sacralized L5

procedure pain is reproduced with this test current, a test voltage is applied to ensure the electrode is remote from the exiting nerve root. The electrode is then heated to 80 °C for approximately 75 s to thermally ablate the median branch. The electrode can be rotated and repeat heating applied. If desired, the electrodes can also be repositioned to ablate the facet capsule itself using bipolar radiofrequency (Jacobson et al. 2017).

4.4 Facet Injections and Aspirations

An alternative approach is to target the facet joint directly with an injection containing a mixture of local anesthetic and corticosteroid. After local freezing of the skin and underlying tissues with a 25-gauge needle, a 22-gauge spinal needle is advanced into the facet joint under either CT or fluoroscopic guidance. If using fluoroscopy, the tube is slightly angled so the articular surfaces of the joint are parallel to the X-ray beam. Overangulation can result in visualization of the anterior aspect of the fact joint, which should be avoided. Also, review of previous cross-sectional imaging is extremely helpful in determining the amount and direction of angulation required, especially in performing facet injections where there are prominent osteophytes posteriorly. Entry at the inferior recess of the facet joint is typically easiest in patients with advanced facet arthropathy. If there are osteophytes interfering with entry into the joint, navigation under CT may be easier: after an initial limited field of view planning CT, an axial slice through the facet joint is selected for navigation and the spinal needle advanced via a posterior or lateral approach to enter the posterior aspect of the joint (Fig. 7). Rotating the bevel of the needle at the margin of the joint will often enable the tip of the needle to slip into the joint space. Use of CT fluoroscopy in a "quick check" method can aid in minimizing overall procedure time. In some patients, if the target facet is close enough to the skin, the procedure can be performed using a 25-gauge local anesthetic needle. A typical injection contains a total of 2 mL of injectate: 1 mL of corticosteroid and 1 mL of 0.5% bupivacaine. Other injection mixtures have been tried including platelet-rich plasma, which in a small study provided longer duration efficacy (Wu et al. 2017).

In the setting of a suspected facet septic arthritis, a spinal needle can be navigated into the joint space as described above and aspiration performed to obtain joint fluid for culture and sensitivity. In these situations, active injection of medications into the facet joint must be avoided, especially administration of corticosteroids.

4.5 Surgical Techniques

There are surgical approaches to treatment of facet-mediated pain, including facetectomy and

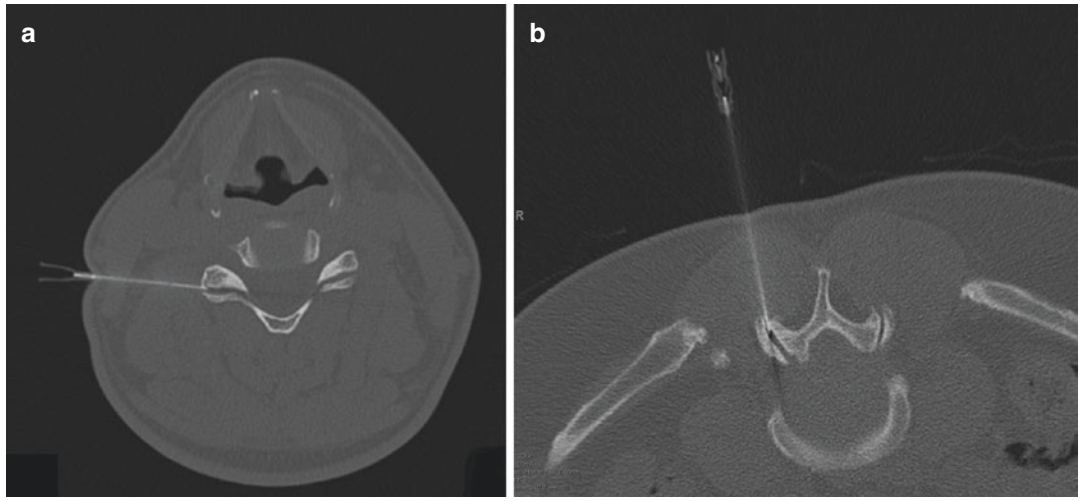

Fig. 7 CT-guided cervical (**a**) and lumbar (**b**) facet injections. The orientation of the facet joint line determines the best direction of approach, laterally for cervical facets and posteriorly for lumbar facets

screw fixation (O'Leary et al. 2018), but the invasiveness of these procedures is not usually justified in the setting of palliative pain management.

5 Effectiveness of Facet Injections

There are varying results on the effectiveness of percutaneous facet joint treatments for pain control. The Facet Treatment Study (FACTS) found a lack of long-term efficacy for intra-articular and median branch blocks compared to placebo, but there was a higher rate of positive responders in the treatment arms suggesting prognostic value before RFA (Cohen et al. 2018) A randomized controlled trial of 28 patients comparing corticosteroid and saline facet injections found no significant difference in the need for subsequent radiofrequency neurotomy for pain control (Kennedy et al. 2018). Conversely, a study of 43 patients receiving facet joint injections showed that at 6-month follow-up, 74% had a clinical significant reduction in pain and 62% an improvement in disability (Campos et al. 2019). Another study of 50 patients showed a significant decrease in pain at 1, 2, and 3-month follow-up, regardless of the severity of facet joint osteoarthritis (Kwak et al. 2018).

A Cochrane review of radiofrequency denervation, synthesizing the results of 12 studies on facet joint pain, found moderate evidence for a short-term reduction in pain compared to placebo, and low quality evidence for improvement of function over the short and long term (Maas et al. 2015).

6 Complications of Facet Injections

Facet joint injections overall have a highly favorable safety profile: in a study of 43,000 facet injections, there were no major complications. Minor risks included local bleeding/oozing and intravascular needle position, which occurred in up to 20% of cervical injections (Manchikanti et al. 2012).

Particulate and non-particulate corticosteroids are used for facet injections. The particulate corticosteroids such as triamcinolone acetonide and methylprednisolone acetate are esters that precipitate out of solution after injection and can aggregate to occlude small blood vessels if there is an intravascular injection. The particulate corticosteroids theoretically provide a more sustained anti-inflammatory effect due to slower dispersal of medication, but there is an

associated risk of neural ischemic injury if these particles embolize to an artery supplying the spinal cord. Dexamethasone sodium phosphate is a nonparticulate steroid that, when injected, forms particles much smaller than red blood cells and does not tend to aggregate. As a result of this potential embolic risk, nonparticulate corticosteroids are recommended for spinal injections, particularly in the thoracic and cervical regions (Peckham et al. 2019). This may be less of a risk with truly intra-articular facet joint injections.

There is a risk related to systemic absorption of the corticosteroid in facet injections, particularly if multiple levels are injected in the same session. Following facet injections with triamcinolone, peak serum levels of the medication occur within 24 h, with a terminal elimination half-life of 213 h. Serum cortisol levels were suppressed to less than 30 mg/mL for an average of 4.4 days (Dickson et al. 2017). As a result of this systemic effect, total dose of corticosteroid administration should be considered, especially in the setting of multiple median branch or intra-articular facet joint injections. Common side effects can include mood disturbance, such as agitation, sleep pattern changes, with insomnia occasionally reported, and alterations in serum blood glucose levels. This latter effect is one requiring specific counselling to those patients with non-insulin or insulin-dependent diabetes. Iatrogenic adrenal suppression following epidural and facet injections has been reported (Jani et al. 2019).

Radiation doses from facet injections are very low, averaging 0.1 mSv for fluoroscopic guidance and 0.33 mSv for CT guidance. The use of fluoroscopy or CT guidance did not have an impact on patient outcomes (Dietrich et al. 2019).

7 Conclusion

Facet-mediated pain is a common cause of disability and diminished quality of life, among the adult population at large and those receiving palliative care. Percutaneous treatments, including facet joint injections and median branch radiofrequency ablations, can provide reduction in pain with an excellent safety profile and rapid post-procedure recovery.

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Spinal Nerve Root Blocks

Hong Chou

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Abstract

Selective nerve root block is a commonly performed procedure for targeted injection of anaesthetic agent and steroids for achieving pain relief in the affected neural distribution. It is widely used as a diagnostic tool and therapeutic procedure in non-malignant conditions such as degenerative disc disease. In the palliative setting, spinal nerve root blocks and neurolysis can be employed for neuropathic pain intractable to systemic analgesics, providing improved quality of life in terminally ill patients. Careful patient selection, appropriate choice of therapy, expert technical skills and a multidisciplinary approach are all important requisites to ensure a good outcome for the patient.

Abbreviations

CT	Computer tomography
MR	Magnetic resonance
MRI	Magnetic resonance imaging
US	Ultrasound

H. Chou (✉)
Department of Diagnostic Radiology, Khoo Teck Puat Hospital, Singapore, Singapore
e-mail: Chou.hong@ktph.com.sg

© Springer Nature Switzerland AG 2021

P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_12

1 Introduction

Image-guided selective nerve root blocks are routinely used in the diagnosis and therapy of radicular pain arising from the spinal nerve roots. The vast majority of these are a consequence of degenerative disc disease in the lumbar or cervical spine. In patients under palliative care, nerve root-mediated pain may arise as a consequence of mass effect of primary malignancy or metastatic disease in the axial skeleton compressing on the nerve roots, either within the spinal canal, in the lateral recess, exit foramen, or on the exited extraforaminal nerve roots. They may also be related to treatment, such as post-surgery or due to the secondary effects of chemo- or radiation therapy. The resultant neuropathic pain may be difficult to control with systemic analgesics alone. In some patients, the use of opioids and other pain medications may be limited by their side effects. Nerve root blocks can be utilized to complement these medications, reducing the dosage required and possibly eliminating their use altogether. They may also be employed together with vertebral procedures such as vertebroplasty with or without tumour ablation. With the advent of readily available imaging modalities such as computed tomography (CT) and fluoroscopy, these procedures can now be performed with high accuracy and safety, by interventional radiologists, anaesthesiologists, orthopaedic surgeons, and other pain practitioners.

2 Indications and Patient Selection

Appropriate selection of patients for image-guided nerve root blocks is paramount for achieving high technical success rates and good patient outcomes. A close collaboration with the palliative care team would enable holistic management of the patient. Ideally, each potential case should be discussed in a multidisciplinary meeting which may include palliative care, musculoskeletal intervention radiology, radiation oncology, and anaesthesia experts (Chu et al. 2015).

Cancer pain frequently arises from local mass effect from the primary tumour mass or metastatic lesions. These cause physical compression with associated inflammation and oedema on both neural and non-neural tissues. Other causes of pain in cancer patients include paraneoplastic syndrome causing peripheral neuropathy, treatment related—either post-surgical or chemotherapy, or other associated conditions as a consequence of immune-suppression such as infection (Scott-Warren and Bhaskar 2014). Most patients referred for interventional pain management would already be on conventional analgesics, usually taken orally or delivered trans-cutaneously. 10–20% of these patients have pain that remains difficult to manage and would benefit from some form of interventional technique (Scott-Warren and Bhaskar 2014; Jadad and Browman 1995). Neuropathic pain poses a particular challenge for the pain team and are often resistant to or require high doses of opioids for management, with consequent side effects (Fallon 2013). It is in these situations where a targeted nerve block can provide symptomatic relief for the patient and reduce dependence on other pharmacologics such as opioids with their accompanying side effects.

Patient assessment begins with obtaining a good clinical history and physical examination. Knowledge of the underlying malignant disease process, the prognosis, and life expectancy of the patient would help to determine the appropriateness of treatment and choice of technique. A simple nerve block may provide relief for a few weeks whereas neurolytic procedures may provide analgesia for up to a few months. For patients with a longer life expectancy, longer acting interventions such as continuous infusion of pain medications via an epidural catheter or implantable drug delivery devices should be offered (Tay and Ho 2009).

When interviewing the patient, the nature, location, and severity of the pain experienced should be elicited. The pain should be primarily radicular in nature to fully benefit from a nerve root block. Conversely, pain localized to the axial skeleton only is usually secondary to local disease without neurological involvement. A nerve

root block would not be effective in pain control in these cases (Palmer 2016). The distribution of pain should correspond to a specific nerve root innervation. This can be confirmed on physical examination by identifying patterns of weakness and loss of sensation in the affected dermatomes and myotomes due to nerve damage. Assessment should also be made on the patient's response to current pain medications as a baseline for reference post-procedure.

Cross-sectional imaging studies such as computed tomography (CT) scan or magnetic resonance imaging (MRI) are important for identifying the cause of pain, the extent of the lesion causing neural compression as well as for pre-procedure planning. Imaging findings should be correlated with the distribution of radicular pain and findings from neurological examination.

Consent taking is an integral part of the pre-procedural process. The interventional technique should be clearly described to the patient. Details which should be made known to the patient include positioning, site of injection, medications used, and expected duration of action and symptom relief. Potential complications and side effects should be discussed and are summarized in Table 1. For example, motor dysfunction or paralysis of affected muscle groups which are usually transient. Bleeding and infection are rare complications and readily preventable when adequate precautions are taken. Contraindications to the procedure such as drug allergies and anticoagulation therapy should be sought during the interview (Palmer 2016). Consent taking offers an excellent opportunity to discuss and manage the patient's expectation of what the procedure aims to achieve and to set realistic treatment endpoints.

3 Contraindications and Limitations

Contraindications are generally relative rather than absolute. These include specific allergies to contrast agent and anaesthetic drugs, local infection over the injection site, severe coagulopathy, or anticoagulation therapy. All patients should be screened with coagulation profile with normal values for platelet count, prothrombin time (PT), and international normalized ration (INR) prior to the procedure. Aspirin should be withheld for 3 days, Plavix and Coumadin (Warfarin) 5 days before the procedure.

The inability to maintain proper positioning for the procedure can be a significant problem in this group of patients. Some patients may not be able to lie prone for procedures requiring a posterior approach. Modification of technique in a position comfortable for the patient, such as an oblique or lateral decubitus posture, may be required for the procedure to be performed. Adequate analgesics before and during the procedure will assist in maintaining a suitable position and minimize patient movement.

Some patients may have multilevel disease involving several nerve roots. A single nerve root procedure may provide only partial relief of symptoms. In these cases, an epidural injection may be the preferred procedure.

Most patients will experience pain relief immediately following the procedure due to the rapid effects of the anaesthetic agent administered. Patients may experience numbness and even muscle weakness in the affected neural distribution. These usually transient and wear out after 2–6 h. The anti-inflammatory effect of injected corticosteroids requires 12–24 h to take effect and only reach their maximum efficacy

Table 1 Potential side effects of nerve root blocks

During procedure	Early (<24 h)	Late (>24 h)
Pain/neural damage	Pain	Infection
Haemorrhage/vascular damage	Haemorrhage	Flushing reaction to steroids
Contrast reaction	Motor weakness	Uncontrolled blood sugars
Vasovagal reaction	Paraesthesia	
Dural puncture	Headache	

after 4–6 days. The efficacy of the injection varies with disease severity and may last anywhere from 2 to 8 weeks. Neuro-ablative techniques or continuous neuraxial drug infusions should be considered for more prolonged symptom relief.

4 Techniques

4.1 Modalities and Equipment

4.1.1 Needles

Spinal nerve root blocks are typically performed with a 22G spinal needle. This offers a good balance between stiffness and bore size, allowing for accurate placement with minimal trauma. A standard 3.5-inch needle is usually sufficient for most spinal nerve blocks. A longer needle may be required to reach deeper structures and should be provisioned for during pre-procedure planning. A short extension tubing is helpful to prevent unwanted radiation exposure to the hand and inadvertent needle displacement during injection.

For interlaminar spinal epidural injections, a specialized epidural needle with a modified Tuohy or Crawford type tip is used for access to the posterior epidural space. The tip is designed to resist dural penetration while maintaining the ability for directional steering.

A smaller 22G needle may be more suitable for cervical or thoracic injection due to the potential risk of cord injury. Larger Tuohy needles can be used (20G–18G) in the mid to lower lumbar region.

4.1.2 CT vs. Fluoroscopy Guided

Fluoroscopic guidance is usually sufficient for most spinal nerve blocks, especially for routine injections for degenerative disc disease. Advantages of fluoroscopic guidance include ready availability, multiplanar angulation, lower radiation dose, real-time visualization of contrast injection, and reduced procedure time in uncomplicated cases.

CT guidance is preferred for cases where visualization under fluoroscopy may be impaired by overlapping bones, presence of implants, large osteophytes, or anatomical distortion due to tumour masses or bony deformities. It allows for more precise needle placement and targeted injection in these situations (Chandra 2013; Koizuka et al. 2014).

CT is also the preferred modality for cervical nerve root injections as it enables visualization of vascular anatomy, particularly of the vertebral arteries which lie near the injection site.

Some imaging units are able to combine the benefits of both modalities by using conventional fluoroscopy in combination with cone beam CT. Rotation of the flat panel detector enables the operator to obtain a CT image for accurate needle placement. The subsequent injection can then proceed under fluoroscopic guidance (Orth et al. 2008).

4.1.3 Planning

Pre-procedure planning is paramount for achieving treatment success and avoiding complications.

A review of recent cross-sectional imaging is particularly important in patients under palliative care. Pre-existing tumour lesions may have shown interval increase in size or undergone necrotic or haemorrhagic changes either due to the disease progress or treatment-related changes. There may be associated erosions or destruction in the adjacent bony structures. These changes will further alter the local anatomy at the site of injection and affect the feasibility of the procedure as well as the selection of optimal approach.

A review of previous whole spine MR scout images will allude to the presence of transitional spinal anatomy which must be taken into consideration to avoid wrong level intervention.

4.2 Medications

Medications used in nerve root blocks are usually a combination of corticosteroids and analgesic agents. Commonly used agents and dosages are summarized in Table 2.

Corticosteroids are anti-inflammatory agents which supress the inflammatory pathways responsible for radicular and axial pain. Both

Table 2 Corticosteroid and Anaesthetic dosage for spinal injections

Procedure	Corticosteroid	Dosage	Anaesthetic	Dosage
Cervical nerve root block	Dexamethasone 4 mg/mL	8–12 mg (2–3 mL)	Bupivacaine 0.25–0.5%	2.5–5 mg (1 mL)
			Lidocaine 0.5–2.0%	5–20 mg (1 mL)
Thoracolumbar nerve root block	Dexamethasone 4 mg/mL	8–12 mg (2–3 mL)	Bupivacaine 0.25–0.5%	5–20 mg (1–8 mL)
	Methylprednisolone 40 mg/mL	20–80 mg (0.5–2.0 mL)	Lidocaine 0.5–1.0%	10–20 mg (1–4 mL)
	Triamcinolone 40 mg/mL	20–40 mg (0.5–1.0 mL)		
	Betamethasone 3 mg/mL	6–9 mg (1.0–1.5 mL)		
Lumbar epidural spinal injection	Methylprednisolone 40 mg/mL	40–120 mg (1–3 mL)	Bupivacaine 0.25–0.5%	15–40 mg (3–8 mL)
	Triamcinolone 40 mg/mL	60–120 mg (1.5–3 mL)	Lidocaine 0.5–1.0%	15–40 mg (3–8 mL)
	Betamethasone 3 mg/mL	9–18 mg (1.5–3 mL)		

chemical irritation and mechanical forces can incite an inflammatory response mediated largely by the release of cytokines and prostaglandins which are part of the physiologic inflammatory cascade. Corticosteroids provide pain relief by essentially blocking neural transmission along these pathways (Rydevik et al. 1984; Robinson and Brown 1991).

Corticosteroids for purposes of nerve root blocks can be broadly classified into particulate and non-particulate agents. Particulate agents are the more commonly used form and include triamcinolone acetonide, betamethasone acetate, and methylprednisolone acetate. These agents contain insoluble compounds in suspension and thus have a cloudy appearance. Non-particulate agents on the other hand consists of soluble compounds and have a clear appearance. These include dexamethasone sodium phosphate and betamethasone sodium phosphate (Derby et al. 2008). Non-particulate agents are advocated for cervical nerve blocks as there are reports of neurologic complications possibly related to intra-arterial embolic phenomena from injection of particulate steroids (Scanlon et al. 2007; Baker et al. 2003). Non-particulate corticosteroids have shown to be of comparable efficacy compared to particulate steroids for the purposes of nerve root injections.

Corticosteroids have a delayed onset of action, usually starting at 12 h post injection and gradually peaking at 4–6 days post injection. Concurrent injection with anaesthetic agents, such as Lidocaine, Bupivacaine, or Ropivacaine which have an almost immediate onset of action, will enable evaluation of pain relief soon after injection. The effects however are short-lived and often do not persist beyond 6–8 h depending on the agent used (Midia and Dao 2016).

To achieve a longer duration of pain relief, drugs may be infused via a percutaneously inserted epidural or intrathecal catheter attached to an external syringe pump. Implanted intrathecal drug delivery devices serve the same function, delivering drugs directly into the intrathecal space. Opioids, most commonly Morphine, are often employed for this purpose. Hydromorphone is the next most common spinal opioid agent and is recommended by some as a second-line agent. Other opioids used less frequently include fentanyl, sufentanil, meperidine, and methadone (Sloan 2007). The addition of local anaesthetics, most commonly Bupivacaine, have been shown to have a potent synergistic effect when used together with opioids (Nitescu et al. 1998; Du Pen et al. 1992). Their combined use also reduces both the dose

and dose progression of opioids when administered intrathecally (van Dongen et al. 1999). Other adjuncts such as Ketamine, an alpha-2-adrenergic agonist and Clonidine, an *N*-methyl-D-aspartate receptor antagonist, may also be used in tandem for additional pain relief (Eisenach et al. 1995; Yang et al. 1996). The proper titration and dosing of these agents for epidural or intrathecal use requires expert knowledge of the pharmacologic properties, dosing requirements, and side effects of the various agents, and are usually managed by pain specialists such as anaesthetists. Further details pertaining to neuraxial drug administration have been described in the preceding chapter on epidural interventions.

4.3 Cervical Nerve Root Blocks

Cervical nerve root blocks in cancer patients are indicated for vertebral metastases, Pancoast tumours, or other malignancies in the neck involving the exiting cervical nerve roots. These may be employed along with brachial plexus blocks in the appropriate setting (Vranken et al. 2000).

Cervical nerve root blocks may be performed under fluoroscopic or CT guidance; however, the latter is the preferred modality for accurate needle placement and to reduce the risk of vascular injury or intravascular injection. Various approaches have been described including anterior-lateral and posterior approaches (Wagner 2005; Wald et al. 2012) (Fig. 1).

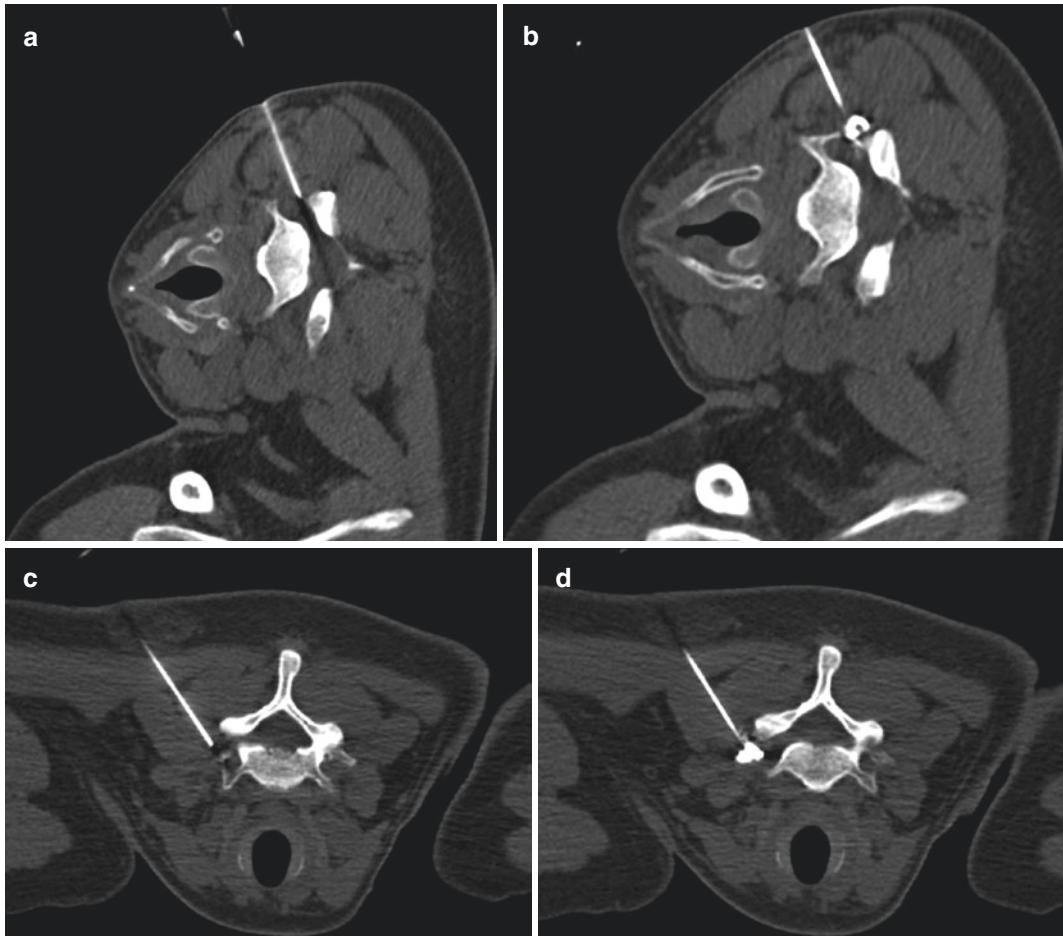

Fig. 1 CT-guided C7 cervical nerve root block. Antero-lateral approach in lateral decubitus position (**a**) before and (**b**) after contrast injection. Posterolateral approach in prone position (**c**) before and (**d**) after contrast injection

There have been rare reports of ischaemic neurologic injuries due to transforaminal injection of cervical nerve roots in recent years. These are postulated to be due to embolic phenomena from inadvertent intravascular injection of particulate steroids into radicular or vertebral arteries (Scanlon et al. 2007; Baker et al. 2003; Rathmell et al. 2015; Huntoon 2005; Hodler et al. 2013). Various techniques have been advocated to mitigate the risk of neurologic injury such as using CT guidance, a posterior approach, extraforaminal needle placement, and the use of non-particulate steroids such as Dexamethasone Sodium Phosphate (8–12 mg, 4 mg/mL) (Huntoon 2005; Hodler et al. 2013; Engel et al. 2014). Ropivacaine has been shown to cause the precipitation of steroid compounds when admixed with Dexamethasone (Rathmell et al. 2015), and thus the two drugs should not be used in combination. Injection of iodinated contrast prior to administration of therapeutic drugs documents the extra-vascular location of the needle tip before administering the pain medications.

4.4 Thoracic Nerve Root Blocks

Thoracic nerve root blocks are indicated in cases of neural involvement by metastatic disease to the thoracic vertebra. Pleural disease from lung or pleural malignancies may also involve the exiting thoracic nerve roots and intercostal nerves. Post-thoracotomy pain may also be amenable to intercostal nerve blocks (Wurnig et al. 2002). These typically produce a characteristic pain distribution along the thoracic dermatome which radiates along the ribs to the lateral or anterior chest wall. The nerve root may be targeted using CT or US guidance as it exits at the neural foramen or further distally as an intercostal nerve root block (Fig. 2).

4.5 Lumbar and Sacral Nerve Root Blocks

Lumbar and sacral nerve root blocks are more commonly performed compared to cervical and thoracic nerve blocks. Specific nerve roots may be targeted if the patient's symptoms can be attributed to one or two nerve roots. This enables precise drug delivery directly to the involved nerve root, allowing for superior therapeutic effect with lower drug doses compared to an interlaminar spinal epidural block (Lee et al. 2009). CT or fluoroscopy may be used to guide the injection. In patent foramina, a supra-neural and intra-foraminal placement of the needle tip facilitates epi-radicular flow of injected drugs to the next higher disc level (Pfirrmann et al. 2001). Conversely, an infra-neural positioning of the needle favours dorsal and caudal epidural flow of medications (Park et al. 2011). In cases of foraminal stenosis preventing a transforaminal approach, extraforaminal needle placement targeting the ventral ramus is acceptable (Palmer 2016). The exited lumbar and sacral nerve roots may also be targeted more distally at the lumbar and lumbosacral plexuses (Figs. 3 and 4).

CT guidance is preferred for sacral nerve blocks due to the oblique course of the sacral foramen which may also be narrowed by malignant soft tissue or bony destruction, making targeting under fluoroscopy challenging.

4.6 Spinal Epidural Injections

Spinal epidural injections form the mainstay of spinal interventions for pain relief. They are indicated when a wider area of pain control is required. Their effects spread bilaterally and across several levels above and below the site of injection. These may be performed at the cervical, thoracic, or lumbar levels, under CT or fluoroscopic guidance. A precise technique is required to accurately place the needle tip beyond the interspinous ligament and ligamentum flavum without penetrating the dura into the thecal sac. The "loss of resistance" technique has been well described as the needle tip traverses from the high-resistance interspinous ligamentous tissues to the low-resistance epidural space. This technique, when used together with fluoroscopic or CT guidance and administration of iodinated contrast to delineate the epidural space, confirms

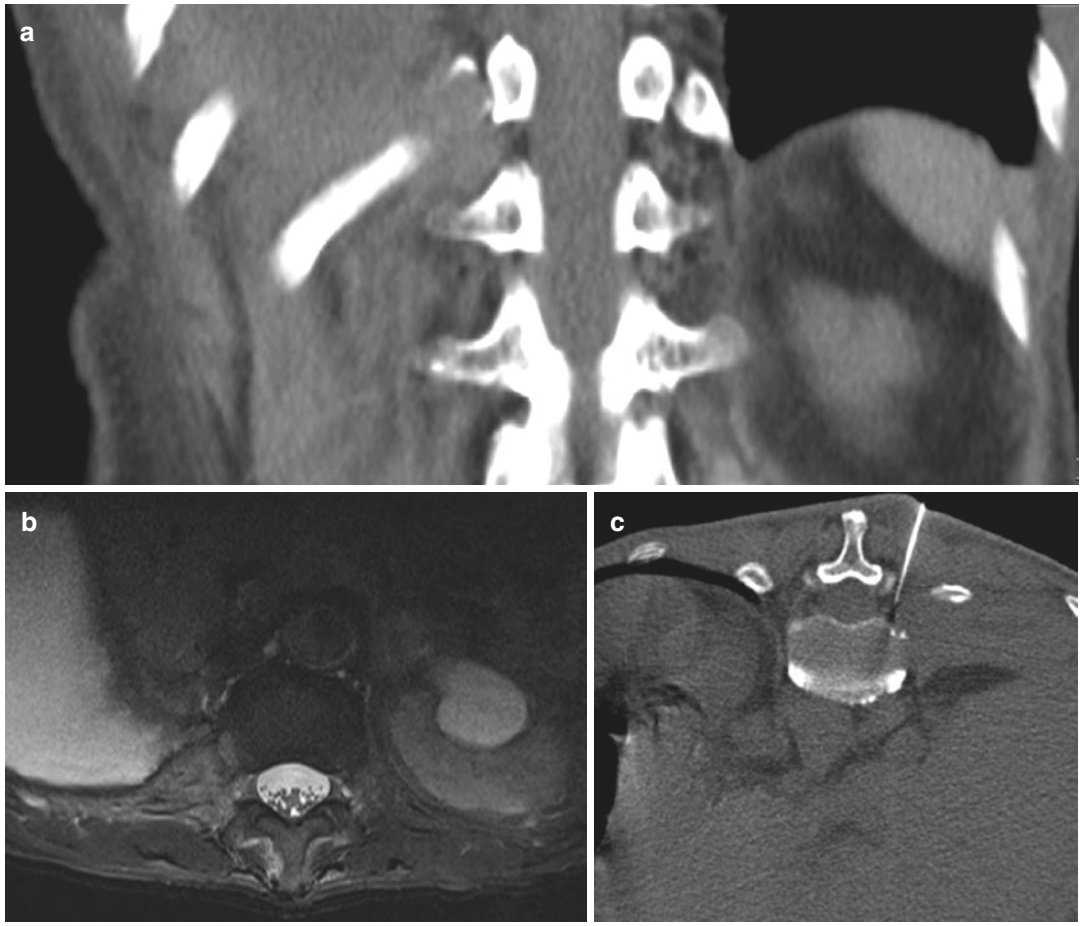

Fig. 2 A 66-year-old man with metastatic lung cancer and right flank pain along T12 dermatome. (**a**) Coronal CT image showing metastatic soft tissue eroding the proximal right 12th rib and extending inferiorly to the right T12 neural foramen. (**b**) Axial T2-W fat-saturated MR image depicting the same mass filling the exit foramen along with a right pleural effusion and incidental note of left hydronephrosis. (**c**) Axial CT image in prone position showing needle placement during CT-guided T12 nerve root block

the appropriate placement of the needle tip prior to injection of medications (Eckel and Bartynski 2009). Intravascular or intrathecal flow of contrast would necessitate withdrawal and repositioning of the epidural needle. In the event of inadvertent dural puncture, manifesting as layering of contrast in the subarachnoid space, subsequent attempts at needle placement should be performed at a separate level or even rescheduled to avoid complications from intrathecal flow of medications (Palmer 2016).

The level of injection selected should be as close to the source of pain as possible while also considering the depth of the epidural space at each level. In patients with previous spinal surgery, the surgical site is best avoided due to the presence of fibrotic scar tissue preventing successful access to the epidural space and risk of intrathecal injection (Eckel and Bartynski 2009).

There are limited studies on the efficacy of cervical and thoracic epidural spinal injections. In the cervical spine, the most capacious epidural space at C6-C7 or C7-T1 level is often targeted using a posterior midline approach with a 22G epidural needle. The thoracic spine poses a unique challenge due to the steep angulation of the spinous processes. An oblique interlaminar approach is used to circumvent this.

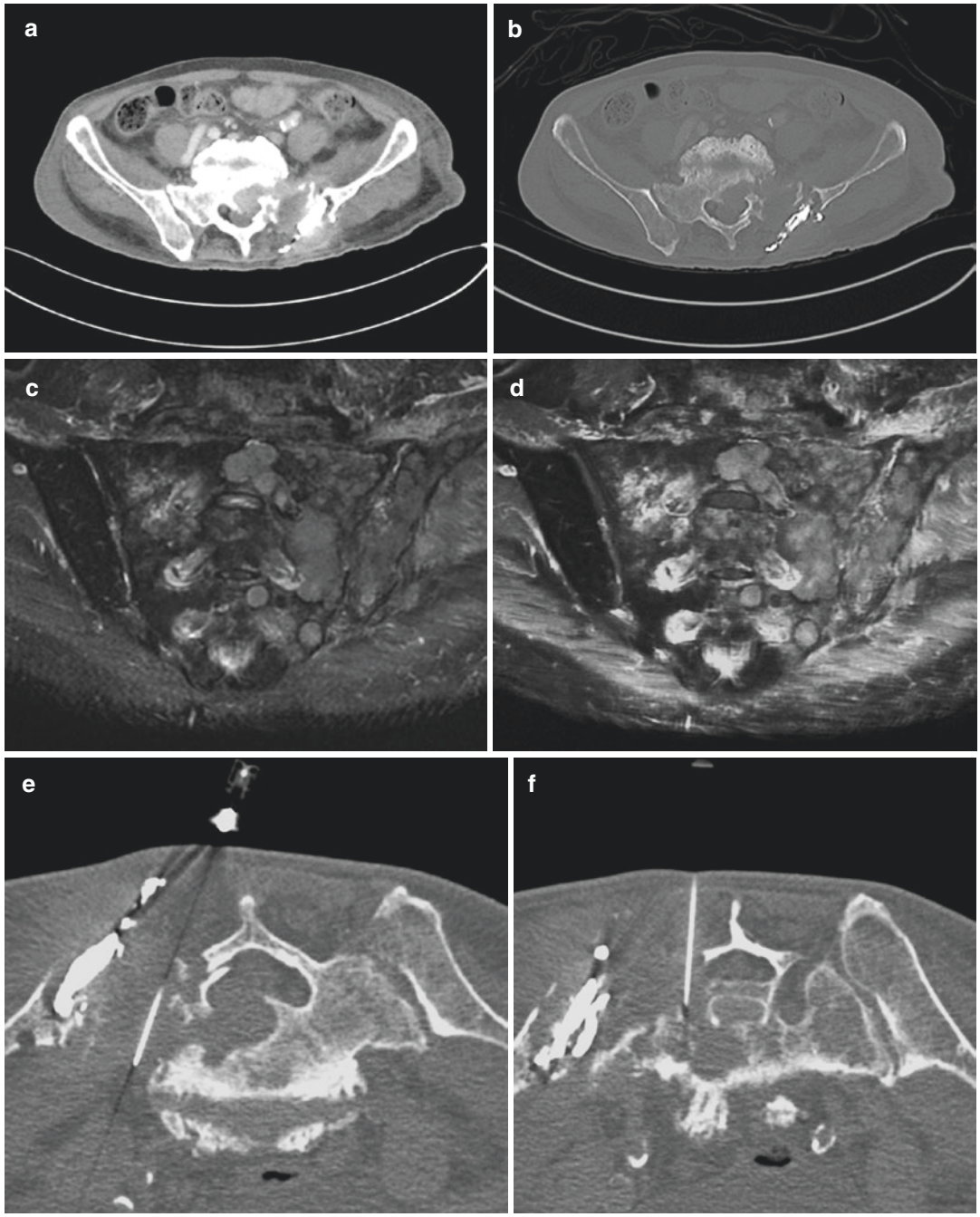

Fig. 3 A 73-year-old man with metastatic lung cancer to the left hemipelvis. Post-contrast axial CT images just below L5-S1 level in (**a**) soft tissue and (**b**) bone windows showing destruction of the left hemi-sacrum with soft tissue impinging on the traversing left S1 and exited left L5 nerve roots. (**c**) Coronal T2-W and (**d**) post-contrast T1-W Fat-saturated MR images showing tumour invading the left S1 foramen. Axial CT images in the prone position showing needle placement for (**e**) L5 and (**f**) S1 nerve root block procedure. Partial visualization of prior cementoplasty in the left iliac bone

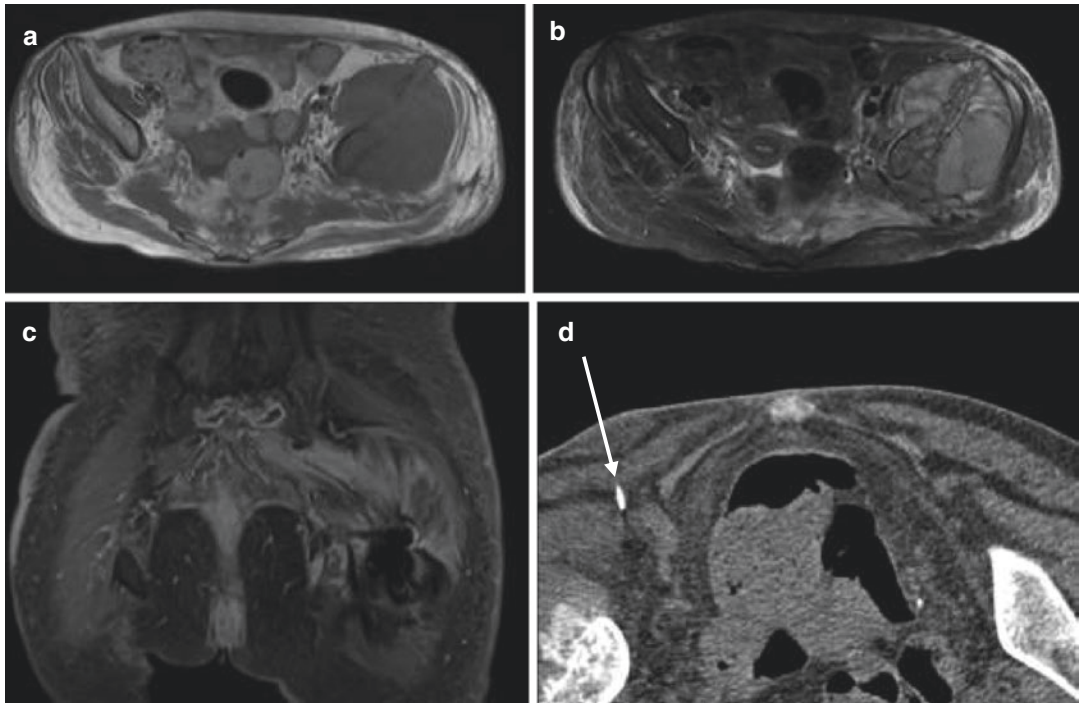

Fig. 4 A 60-year-old woman with large metastatic lesion in the left hip from recurrent adrenal cancer, presenting with severe neuropathic posterolateral upper thigh pain. (**a**) Axial T1-W and (**b**) T2-W fat-saturated MR images showing a large soft tissue mass around the left iliac bone and increased T2-W signal along the left lumbosacral plexus. (**c**) Coronal post-contrast enhanced T1-W fat-saturated image depicts enhancing tumour tissue tracking along the left lumbosacral plexus approaching the sciatic nerve. (**d**) Prone axial CT image showing needle tip position (arrow) for lumbosacral plexus block

Lumbar epidural spinal injections are widely performed, mainly for spinal stenosis. They may be done under CT or fluoroscopic guidance. Biplane fluoroscopy allows the operator to target the midline on frontal projections and accurately assess the needle depth subsequently on the lateral projection. Under CT, an off-midline oblique approach would be preferred due to the angulation of the spinous processes relative to the scan plane. A level caudal to L1 is usually preferred to reduce the chance of cord injury (Fig. 5).

Caudal epidural injections have also been described. In this technique, the epidural space is accessed from the sacral hiatus which typically lies at S4 level, while the dural sac usually terminates between S1 and S2 levels. This allows for epidural injection with low risk of dural puncture (Kao and Lin 2017). Fluoroscopic guidance is the preferred modality, with ultrasound as an alternative (Manchikanti et al. 2004). The midline may be palpated just above the gluteal cleft with the patient in prone position. The sacral hiatus is seen as an abrupt step-off at S4 level on lateral fluoroscopy (Landers and Aprill 2011). An epidural needle is directed at a 45-degree angle to enter the sacral canal. The tip is then advanced to no higher than S3 level. Injection of 5–6 mL of iodinated contrast is performed to outline the epidural space and confirm epidural placement of the needle tip. Subsequently, a mix of corticosteroids and anaesthetic agent may be administered (Johnson et al. 1999). A larger volume of injectate is often required to maximize the distribution of anaesthetic effect.

Neuraxial drug delivery can also be achieved by placement of an indwelling epidural or intrathecal catheter attached to an external syringe pump or implantable device. This allows for continuous delivery of opioids, anaesthetics, and other medications for prolonged pain relief.

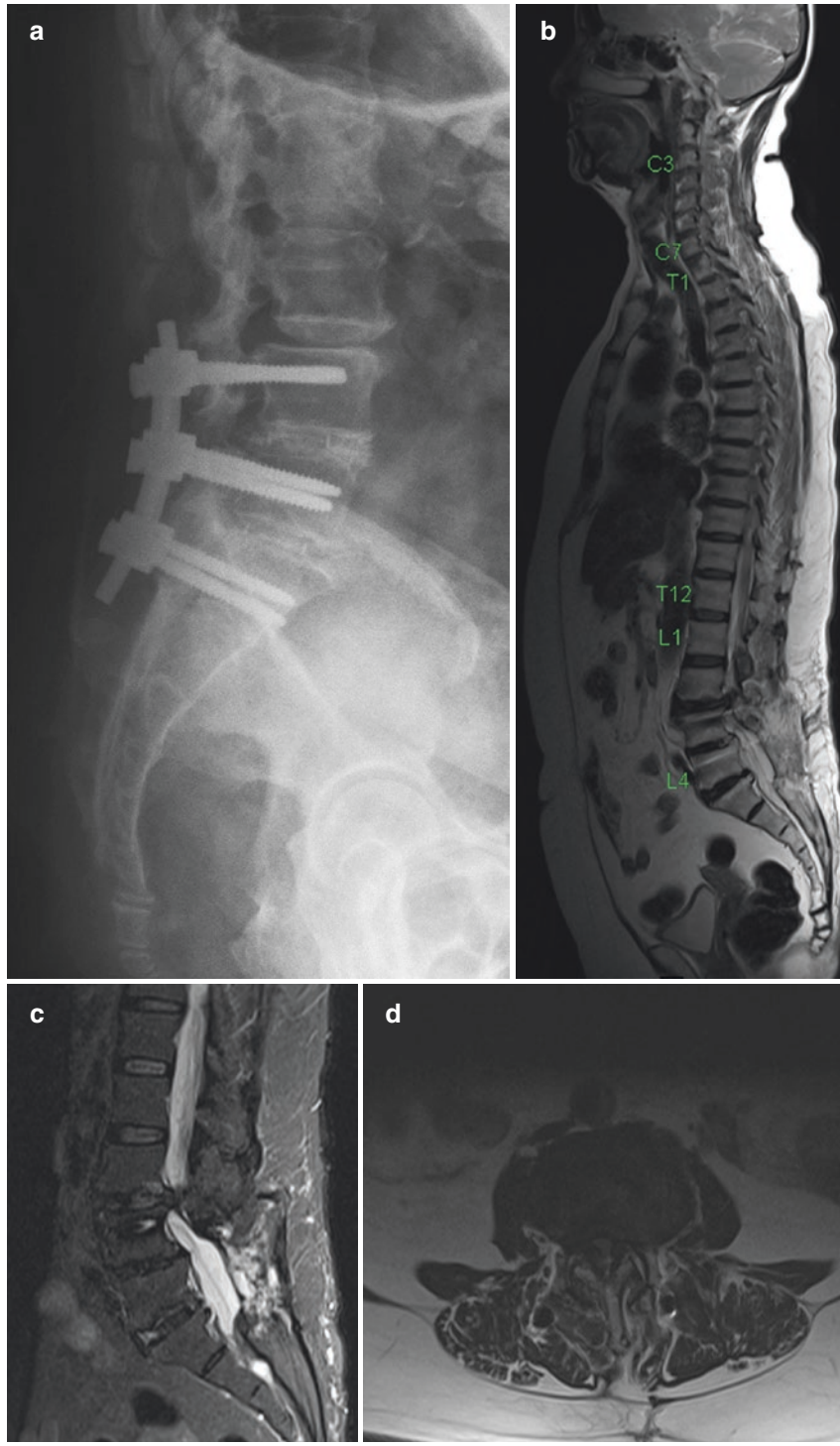

Fig. 5 A 77-year-old woman with previous L3 to L5 laminectomy and posterior instrumentation, presenting with bilateral lower limb radiculopathy. (**a**) Frontal radiograph of the lumbar spine with implants in place. (**b**) Sagittal MR scout image demonstrates transitional spinal anatomy with sacralization of L5. (**c**) Sagittal T2-W fat saturated and (**d**) axial T2-W MR images show severe spinal stenosis at L2-L3 disc space with crowding of the cauda equina. Axial CT images at L2-L3 level depicting needle position (**e**) before and (**f**) after injection of iodinated contrast agent, followed by subsequent epidural injection of anaesthetics and steroids

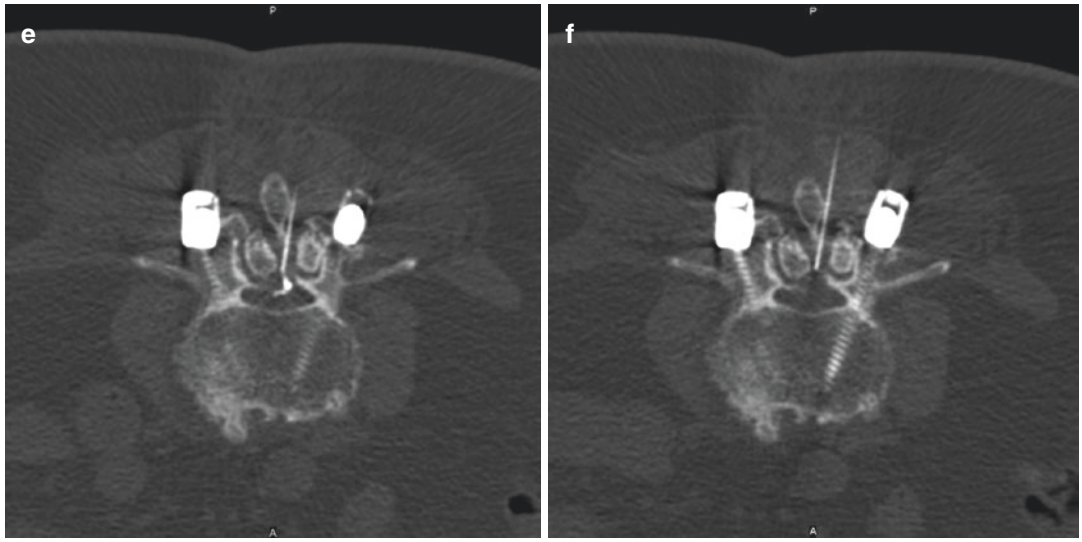

Fig. 5 (continued)

Improvements in equipment used for these techniques in recent years have largely obviated the need for destructive neuro-ablative procedures.

5 Post-procedure Care and Follow-Up

Pain assessment can be performed and documented immediately following the nerve block procedure. This serves as both a diagnostic and prognostic indication of analgesic effect. Reinforce the expected timeline for anaesthetic and steroid effects to the patient. Patients may experience transient weakness or paraesthesia in the affected nerve distribution and should be monitored for an appropriate time following the procedure. Proper assessment of adequate motor strength for weight bearing and ambulating is necessary prior to discharge. Instructions to patients would include activity restrictions such as not operating a motor vehicle or machinery for the remainder of the day of the procedure. The patient should be advised to monitor for potential side effects such as bleeding or inflammation at the injection site. If anticoagulants had been discontinued in preparation for the procedure, clear instructions should be given for restarting them. Diabetic patients would need to monitor their blood glucose level closely due to potential systemic absorption of injected corticosteroids.

A pain diary is helpful for documenting pain response over the course of the next few weeks. Symptoms normally continue to decrease for 2–3 weeks following the procedure. The effectiveness of corticosteroids will begin to dissipate after 6–8 weeks (Palmer 2016). Depending on treatment response, a repeat injection may be indicated. Concurrent oral or parenteral pain medications may be titrated by the multidisciplinary pain team according to the pain response. In cases where there is disease progression resulting in worsening of neuropathic pain, alternative therapies such as epidural drug infusions or neuro-ablative techniques should be considered.

6 Conclusion

Spinal nerve root blocks are a small but important component in the wide range of interventions for the management of neuropathic pain in palliative care. Careful selection of patients along with detailed assessment of pain will enable the practitioner to select the most appropriate intervention. The ready availability of imaging guidance enables precise needle place-

ment in a wide range of scenarios. Proper pre-procedure planning, patient preparation, and appropriate choice of pain medications reduces the potential side effects and complications while ensuring a high rate of technical success. The interventionist, working as part of the multidisciplinary care team, plays a critical role in pain management with the ultimate goal of improving the quality of life in the terminally ill patient. As the rallying cry of palliative care goes, "To cure sometimes, to relieve often, and to comfort always".

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Nerve Blocks (Non-spinal)

Eelin Tan, Sum Leong, and Chow Wei Too

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Abstract

Nerve blocks are valuable adjuncts as intra-procedural analgesia for cancer patients. They may also provide intermediate to long-term management of cancer-related pain when used alongside neural modulation, chemical or thermal ablation. This chapter provides an overview of image-guided peripheral nerve and plexus interventions relevant in palliative care. Nerve root and autonomic blocks are addressed in chapters "Spinal Facet Injections for Palliative Pain Management" and "Nerve Blocks (Non-spinal)", respectively.

E. Tan (✉) · S. Leong · C. W. Too
Department of Vascular and Interventional Radiology, Singapore General Hospital, Singapore, Singapore
e-mail: eelin.tan@mohh.com.sg; leong.sum@singhealth.com.sg; too.chow.wei@singhealth.com.sg

© Springer Nature Switzerland AG 2021

P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_13

Abbreviations

CT	Computer tomography
LA	Local anesthetic
MRI	Magnetic resonance imaging
MWA	Microwave ablation
PNB	Peripheral nerve block
PRF	Pulsed radiofrequency
RFA	Radiofrequency ablation
US	Ultrasound

1 Introduction

Interventional radiologists are integral in the management of palliative patients requiring minimally invasive image-guided pain interventions in the era of multidisciplinary cancer care (Chu et al. 2015). The European Society for Medical Oncology (ESMO) recommends invasive therapies for pain refractory to conservative therapy and for patients with dose-limiting opioid-related side effects (Fallon et al. 2018). While there are no controlled studies on peripheral nerve blocks for cancer pain, multiple case studies have reported satisfactory pain relief and good safety profiles (Klepstad et al. 2015). Early use of nerve blocks can also improve quality of life (Lipton 1989; Amr and Makharita 2014) and facilitate physical therapy (Chambers 2008).

Cancer-related pain can arise from direct invasion of nerves, mass effect or pathological fracture (Caraceni and Shkodra 2019). Patients may also experience treatment-related pain from surgery (e.g., post-thoracotomy or mastectomy pain), chemotherapy or radiation therapy (Mehio and Shah 2009). Nerve blocks with LA provide short-term pain relief by temporarily disrupting nerve conduction. Neural modulation with PRF and neurolysis using chemical or thermal means provide intermediate to long-term pain relief, respectively. US, fluoroscopy and CT are routinely used to guided pain interventions and minimize complications.

Many peripheral nerves can be targeted for pain control in palliative care. These include cranial nerve blocks for locally invasive nasopharyngeal and oropharyngeal cancers (Sist 1997; Bedder and Lindsay 1989; Kohase et al. 2004); intercostal nerve blocks for rib metastases +/− pathological fracture (Wong et al. 2007); brachial plexus blocks for Pancoast tumors, axillary tumors, and pathological upper limb fractures (Vranken et al. 2000; Neill 1979; Zinboonyahgoon et al. 2015); and femoral and obturator nerve blocks for painful hip metastases (Stone and Matchett 2014).

2 Indications

Pain should be localized to a peripheral nerve or plexus territory (Chambers 2008). Both somatic nociceptive and neuropathic pain can be interrupted (Haroutounian et al. 2014; Kurita et al. 2019). Thorough clinical evaluation is essential to clearly delineate, characterize and quantify the pain. Pre-procedural imaging is helpful for identifying organic cause and planning interventional approach.

Procedures may be diagnostic, prognostic or therapeutic. A diagnostic block with short-acting LA can first be trialled to confirm that the targeted peripheral nerve is responsible for symptoms. A prognostic block with long-acting LA can predict and extrapolate the efficacy of pain relief and tolerability of potential side effects like numbness and paresis. The durability can be accentuated using neural modulating methods such as PRF (Chua et al. 2011). Therapeutic blocks are usually accomplished with destructive neurolysis in the setting of malignant pain but can also be accomplished with LA (Deer et al. 2014).

Non-destructive nerve blocks can also be used to provide regional anesthesia during interventional procedures such as biopsy, tumor ablation and tumor embolization (Midia and Dao 2016).

3 Contraindications

General contraindications include active infection at the intervention site, intervention at a non-compressible anatomic location in patients with uncorrected coagulopathy, thrombocytopenia or on anticoagulant therapy, drug allergy, inability

to sustain suitable position during intervention, patient refusal and lack of capacity (Simpson 2011; Horlocker et al. 2010).

4 Therapeutic Options

Nerve blocks, neural modulation and neurolysis are discussed in this section. Key consideration and differences include the following:

1. Analgesic effect from neurolysis is less profound compared to LA (Benzon et al. 2008).
2. Both LA and neurolysis will produce numbness together with pain relief.
3. Most peripheral nerves possess both afferent and efferent neurons. LA may spare motor blockade at low concentration because of differential nerve sensitivity to LA (Deer et al. 2014; Vadhanan et al. 2015), while motor blockade often cannot be avoided with neurolysis (Benzon et al. 2008).
4. Although neurolysis is neurodestructuve, therapeutic effect is not permanent, as the nerve is not completely destroyed. Pain relief usually lasts for weeks to months depending on ablative modality and nerve repair, after which pain can recur (Choi et al. 2016).
5. Following neurolysis, complications like neuritis and neuroma may manifests in a matter of months. Pain from these complications may be worse than the original pain. Neurolysis is therefore most suitable in terminal patients with short-life expectancy who may not live long enough for such complications to develop (Deer et al. 2014).

4.1 Local Anesthetics

LAs reversibly block voltage-gated sodium channels and influx of sodium ions, preventing depolarization and nerve signal conduction (Deer et al. 2014; Vadhanan et al. 2015). Larger myelinated A alpha and A gamma nerve fibers (motor and proprioception) are less sensitive to LA compared to small lightly myelinated A delta nociceptors (fast prick and sharp pain) and autonomic nerve fibers. Differential sensitivity of nerve fibers to LA is concentration dependent and is lost at high concentrations (Deer et al. 2014; Vadhanan et al. 2015).

Administration of LA may be single injection, intermittent injection or continuous infusion depending on clinical indication. The most commonly used agents are lidocaine, bupivacaine and ropivacaine, all of which belong to the amino-amide group (Deer et al. 2014). Important properties are summarized in Table 1. Additives may be used in conjunction with LA (Table 2). For instance, bicarbonate 8.4% hastens speed of onset and decreases injection pain, while adrenaline, dexamethasone, buprenorphine, tramadol, clonidine, and magnesium prolong duration of action (Midia and Dao 2016).

Table 1 Properties of commonly used LAs (Deer et al. 2014; Duke 2011)

	Group	Relative potency[a]	Onset[b]	Duration of action[c] (min)	Max dose with/without adrenaline	
					By body weight (mg kg^{-1})	Not to exceed (mg)
Procaine 1–2%	Ester	1	Slow	Short (20–30)	7/10	500/600
Chloroprocaine 1–2%	Ester	1	Fast	Short (15–30)	10/14	800/1000
Lidocaine 0.5–1%	Amide	2	Fast	Intermediate (30–60)	4.5/7	300/500
Mepivacaine 0.5–1%	Amide	1.5	Fast	Intermediate (45–90)	5/6.6	300/500
Prilocaine 0.5–1%	Amide	2	Fast	Intermediate (30–90)	6/9	350/550
Bupivacaine 0.25–0.5%	Amide	8	Intermediate	Long (120–240)	2/2.5	175/200
Ropivacaine 0.2–0.5%	Amide	8	Intermediate	Long (120–240)	3/4	200/250

[a]Dependent on lipid solubility; highly lipid soluble molecules may sequester in adipose tissue
[b]Dependent on pKa
[c]Dependent on protein-binding affinity

Table 2 Common perineural additives to LA

	Dose[a]	Effect(s) on LA	Remarks
Bicarbonate 8.4%	1 mL of bicarbonate 8.4% per 10 mL of lidocaine 2%	Decreases injection pain; hastens speed of onset	LA can precipitate if excessive bicarbonate is added, especially for bupivacaine
Adrenaline 5–10 μg/mL (1:100,000–1:200,000)	0.5–1.0 μg/kg	Prolongs duration of action	Vasoconstrictive effect of adrenaline warrants caution in patients with risk of tissue ischemia (peripheral vascular disease, diabetes, blocks in finger/toes)
Dexamethasone	4–10 mg	Prolongs duration of action	
Buprenorphine	0.3 mg	Prolongs duration of action	
Tramadol	100–200 mg	Prolongs duration of action	Equivocal evidence for use in PNB
Clonidine	0.5–1.5 μg/kg	Prolongs duration of action; potentiates analgesic effect	Associated with hypotension, fainting, sedation, and bradycardia
Magnesium	100–150 mg	Hastens speed of onset; prolongs duration of action	

[a]Doses for use in PNBs

Tips for safe injection Following needle advancement under image guidance, it is important to aspirate for blood prior to block administration to avoid intravascular injection. Similarly, needle repositioning is required when resistance, pain or parasthesia is encountered, which may suggest intrafascicular location of the needle tip (Midia and Dao 2016).

Medical considerations include dose reduction in elderly patients and patients with liver or renal disease (amides are metabolized in the liver and excreted in urine) and avoidance of bupivacaine in patients with heart disease (association with cardiotoxicity) (Deer et al. 2014; Midia and Dao 2016). Early signs of acute LA toxicity include circumoral or tongue numbness, metallic taste, tinnitus, dizziness, and drowsiness, while cardiorespiratory symptoms include hypotension, cardiac arrhythmia, bradycardia, cardiac and respiratory arrest (Sekimoto et al. 2017). If systemic toxicity occurs, airway management and stabilization should be the first priority. Lipid emulsion infusion can be commenced once the patient is stable (Sekimoto et al. 2017).

4.2 Thermal Neurolysis

Thermal neurolysis can be achieved with cold (cryoablation) or heat (conventional RFA or MWA). Both allow concurrent tumor ablation, useful in situations where tumor has infiltrated into or compressed on nervous structures. Therapeutic duration ranges from weeks to months depending on ablative modality and nerve repair (Choi et al. 2016).

Cryoablation Cryoablation makes use of the Joule-Thompson effect, where by rapid cooling occurs when high-pressured gas expands to a low-pressure state across a valve. Cryoneurolysis requires at least −20 °C (Wray and Walls 2019). Current cryoprobes can reach temperatures of −40 to −70 °C at the innermost isotherm and 0 °C at the edge of the ice ball. Two freeze-thaw cycles are required for tumor ablation, but one cycle may be adequate for neurolysis. Each cycle consists of 2–3 minutes of cryoablation and 30 seconds of active thawing. The probe has to be thawed for at least 2 minutes before withdrawal to avoid local injury. Benefits of cryoablation include less intra-

and post-procedure pain compared to heat-based ablation (Allaf et al. 2005; Thacker et al. 2011; Masala et al. 2011) with only transient initial pain that usually resolves within a minute (Ilfeld et al. 2017) and good visibility of the ice ball (ablation zone) on US, CT and MRI. There is also less risk of neuroma formation and hyperalgesia because nerve epineurium and perineurium remain intact. The main technical disadvantage is that track ablation cannot be done with cryoablation. Logistical downsides include longer procedure times, higher cost and availability. Cryoneurolysis is the preferred modality for therapeutic neurolysis at the authors' institution.

RFA RFA makes use of high frequency alternating current passing through a closed circuit within the patient, causing ionic agitation and frictional heat production. Coagulative necrosis occurs above 50–60 °C (Friedman et al. 2004) without preservation of nerve connective tissue (Schoellnast et al. 2011). RFA requires precise control over temperature and time as excessive heat production (>100 °C) induces charring and gas that break the electrical circuit. Compared to monopolar systems which are more common, bi/multipolar systems eliminate the small possibility of skin burns at the grounding pad and are permissible in patients with electrical implants as the current only passes through the electrodes. Water-cooled RFA allows for larger ablation zones. Temperature-controlled systems produce more predictable temperatures and ablation zones than voltage-controlled ones.

MWA MWA makes use of high frequency electromagnetic waves (900–2450 Hz) to agitate water molecules to produce friction and heat inducing coagulation necrosis. Benefits over RFA include higher intra-lesional temperatures, larger ablation volume, faster ablation times and minimal susceptibility to heat sink, producing predictable and uniform ablation zones (Simon et al. 2005). Despite these advantages, reports of MWA for nerve ablation are scarce. A recent cohort study reported good pain relief after US-guided MWA for inguinal neuralgia post-herniorrhaphy (Lee et al. 2019).

4.3 Pulsed Radiofrequency (Neural Modulation)

PRF is more commonly used in chronic non-cancer pain, as it produces neural modulation without tissue destruction. In cancer care, potential candidates include palliative patients who cannot accept the side effect of neurolysis and patients in remission with chronic treatment-related pain.

PRF uses the same technology as RFA but applies short radiofrequency pulses around the nerve target, producing rapid changing electric fields. In contrast to continuous RFA, temperatures are kept low (≤42 °C) and are insufficient for thermocoagulation or sensory denervation (Deer et al. 2014; Choi et al. 2016). Pain relief from PRF is plausibly from alterations in synaptic transmission in response to a patterned electrical stimulus (Cahana et al. 2006), although the exact mechanism remains unclear. The most common pulse duration and pulse frequency are 20 ms and 2 Hz, respectively, with interpulse duration of 480 ms (Chua et al. 2011). The interpulse duration allows heat to dissipate.

Compared to RFA, PRF application is less painful and eliminates the potential side effects of neurolysis, but therapeutic effect is shorter (Deer et al. 2014; Snidvongs and Mehta 2010). A study comparing treatment for post-thoracotomy pain showed that PRF of the dorsal root ganglia provided greater pain relief compared to PRF of the intercostal nerves (Cohen et al. 2006). Targeting the dorsal root ganglia could mitigate motor deficits that may arise from peripheral nerves interventions. Interventionalists should be aware of this alternative.

4.4 Chemical Neurolysis

Pain relief from chemical neurolysis stems from Wallerian degeneration and interruption of nerve transmission (Choi et al. 2016).

Table 3 Comparison of alcohol and phenol for chemical neurolysis (D'Souza and Warner 2019; Kambadakone et al. 2011)

		Alcohol 50–100%	Phenol 5–10%
Mechanism		Lipid extraction, protein precipitation	Protein coagulation
Dilutant		No	Yes; glycerin, saline, or water
Injection pain		Painful; combine with LA	Painless
Onset		Instant	Delayed (15 min)
Duration of action		Relatively longer (12–24 weeks)	Relatively shorter (4–12 weeks)
Physical properties		Low viscosity (rapid spread), hypobaric	High viscosity[a], hyperbaric[a]
Adverse effects	Local	Higher incidence of neuritis	Higher incidence of vascular injury
	Systemic	Disulfiram-like reaction (tachycardia, flushing, inebriation, confusion, etc.)	Nausea/vomiting, seizure, arrhythmia, cardiovascular depression, CNS stimulation

[a]When phenol is diluted with glycerin

Compared to thermal ablation, chemical neurolysis provides less control and is associated with higher risk of non-selective necrosis of both target and non-target tissues. Chemical neurolysis should be performed under conscious sedation to allow biofeedback and image guidance to minimize complications.

The two most common agents, alcohol and phenol, are compared in Table 3. Both have relative advantages and disadvantages. Phenol diluted in glycerin is a high viscosity solution, which may provide better control than low viscosity alcohol; a larger 20-gauge needle will be needed for injection. In terms of safety, alcohol is safe for perivascular injection, whereas phenol has higher affinity for vascular structures. Intravascular injection of both chemicals will, however, produce sclerosis. Neurolytic effect of phenol can only be reliably assessed in 3–7 days after its inherent LA effect has passed. Contrast and LA volumes should be kept low to avoid diluting the neurolytic agent. The technical precautions in the LA section also apply to chemical neurolysis.

5 Techniques for Common Peripheral Nerve Blocks

As a general rule, nerves should be targeted proximal to the site of localized pain (Hochberg et al. 2017). Interventions should also avoid tumor unless concurrent ablation is the goal as anatomy can be distorted, and there is higher risk of bleeding from angiogenesis and risk of seeding (Hochberg et al. 2017).

5.1 Head and Neck

Nerve target: Maxillary nerve.

Anatomy: The maxillary nerve emerges from the foramen rotundum into the pterygopalatine fossa as the most superior nervous structure just above the sphenopalatine ganglion.

Anesthesia distribution: Skin covering the middle one-third of the face (below the orbits and above the mouth), maxillary sinus, nasopharynx, nasal cavity, palate, upper teeth, upper lip, and dura of the middle cranial fossa.

Associated tumors: Nasopharyngeal and oropharyngeal cancers.

Therapeutic options: All.

Image guidance: US, fluoroscopy, or CT.

Position: Supine.

Approach: Lateral approach.

Entry site: Just inferior to the mid zygomatic arch and posterior to the mandibular coronoid process.

Technique: Advanced horizontally through the infratemporal fossa into the pterygopalatine fossa (Fig. 1). Angle the tip superiorly and posteriorly to target the maxillary nerve.

Risks and tips: Inadvertent block of the sphenopalatine ganglion is common as it sits just inferior to the maxillary nerve. Spill into orbit via

inferior orbital foramen can be avoided by addition of contrast media allows visualization of spread of CT and fluoroscopy. If using alcohol, limit to 1.5 mL to avoid spilling into the orbit. Intravascular injection into maxillary vessels can be avoided by use of US Doppler.

Further reading: Mehio, A. K., & Shah, S. K. (2009). Alleviating head and neck pain. Otolaryngologic Clinics of North America, 42(1), 143–159.

Fig. 1 CT-guided maxillary nerve block. Axial CT image showing lateral approach for maxillary nerve block. Entry site is at the mid point of the zygomatic arch. Needle trajectory (dashed arrow) transverses just posterior to the mandibular coronoid process (Co). The tip should aim for the superior pterygopalatine fossa, where the maxillary nerve is located

5.2 Trunk

Nerve target: Intercostal nerve.

Anatomy: Intercostal nerves (T1 to T11) and subcostal nerve (T12) run at the lower margin of each rib as the most inferior structure in the neurovascular bundle.

Anesthesia distribution: T1 and T2 supply their respective dermatomes and contribute to the brachial plexus; T3 to T6 only supply their respective dermatomes; T7 to T11 supply their respective dermatomes, parietal pleura and peritoneum.

Associated tumors: Primary and secondary chest wall and pleural tumors.

Therapeutic options: All.

Image guidance: US is usually sufficient (Fig. 2). CT may be used for concurrent ablation (Fig. 3).

Position: Prone preferred; alternatively lateral decubitus or sitting.

Approach: Posterior approach.

Entry site: Just lateral to spinal column.

Technique: The US probe is held in a sagittal plane. The tip is inserted in-plane to the transducer and advanced to just below the inferior border of the rib (Fig. 2). If using LA or chemical

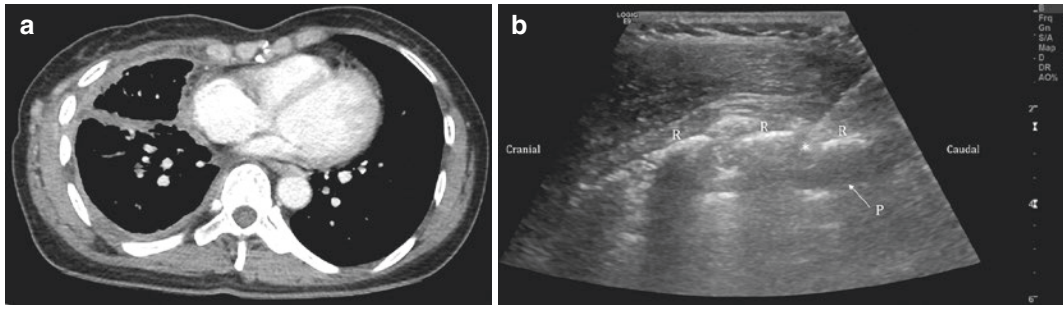


Fig. 2 US-guided intercostal nerve block. (**a**) Axial CT image showing extensive right pleural and chest wall metastases in a patient with primary lung adenocarcinoma and intractable chest wall pain. (**b**) Longitudinal US image shows the in-plane needle tip (*) just inferior to the rib (R). The pleura is seen as a faint hyperechoic line (P). Note how the pleural space is distended by tumor. Intercostal nerve block at the affected thoracic levels was performed with bupivacaine 0.5% and dexamethasone

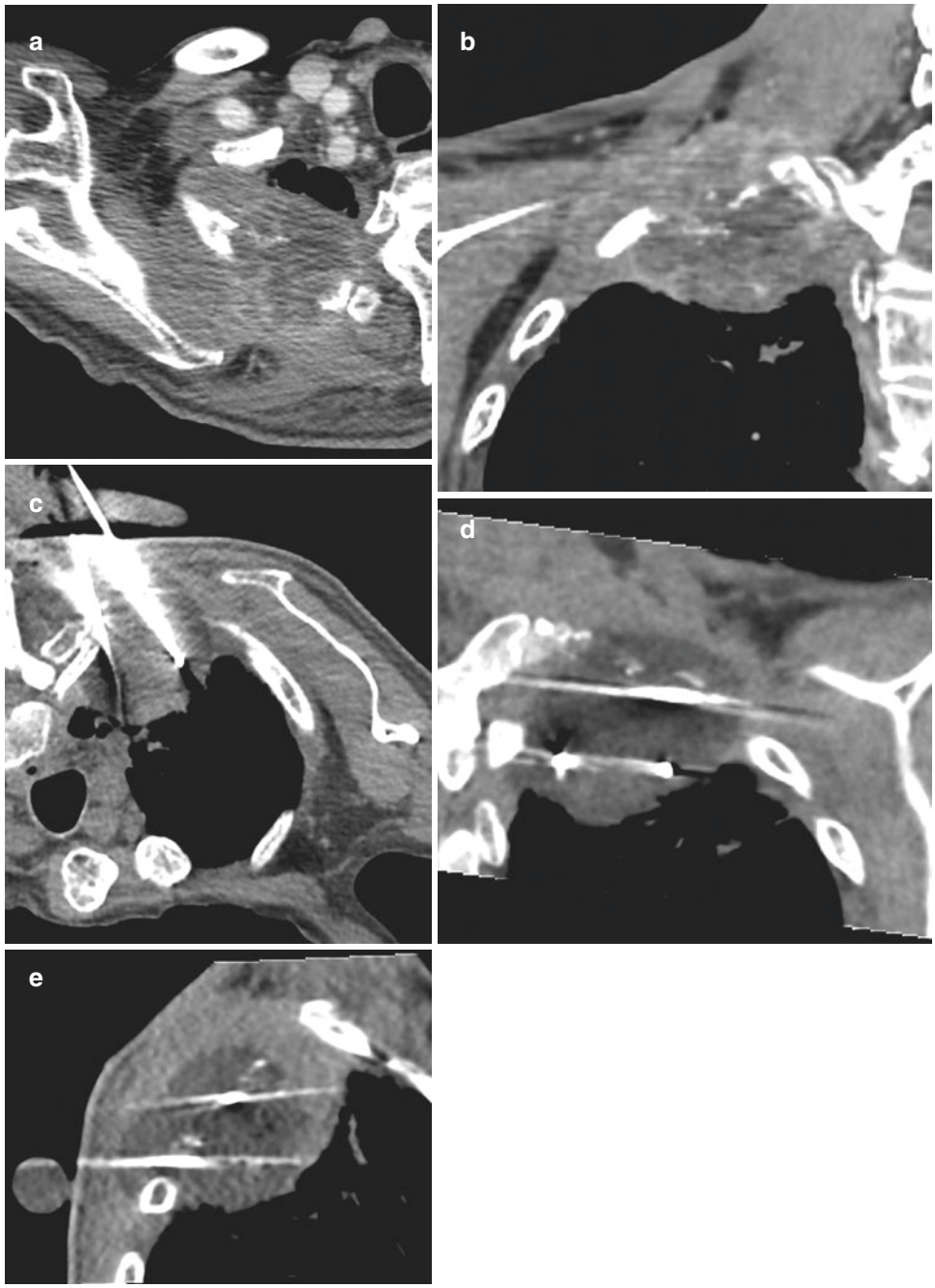


Fig. 3 CT-guided cryoablation of Pancoast tumor and intercostal nerves. (**a**, **b**). Axial and coronal CT images showing right Pancoast tumor (lung adenocarcinoma) with adjacent rib destruction causing chest wall pain. (**c**–**e**). Cryoablation of the tumor was performed with three 14 gauge IceForce cryoprobes (Galil Medical, MN, USA). Axial intra-procedural CT with coronal and sagittal reconstructions shows the ice ball encompassing the tumor and adjacent ribs

agent, negative aspiration is imperative to avoid intravascular injection.

Risks and tips: Pneumothorax is rare under US guidance under an experienced operator. The pleura is seen as a faint hyperechoic line on US (Fig. 2) and should be avoided. Potential LA toxicity stems from high levels taken into the blood via the neurovascular bundle. Patients should be monitored closely following the procedure.

Further reading: Hochberg, U., Elgueta, M. F., & Perez, J. (2017). Interventional analgesic management of lung cancer pain. Frontiers in oncology, 7, 17.

5.3 Upper Extremity

Nerve target: Brachial plexus (interscalene).

Anatomy: The brachial plexus can be blocked at four common locations, as follows (proximal to distal): Interscalene, supraclavicular, infraclavicular and axillary.

Anesthesia distribution: Interscalene block of the brachial plexus will denervate C3 to C7 dermatomes and the shoulder joint.

Associated tumors: Pancoast tumors, axillary metastases, pathological upper limb fractures.

Therapeutic options: All.

Image guidance: US or CT.

Position: Supine or inclined with the head turned to the contralateral side.

Entry site: For interscalene block, entry site is at the base of neck (level of C6).

Approach: Lateral approach.

Technique: The US probe is held in the transverse plane. Tracing up from the supraclavicular brachial plexus (lateral to the subclavian artery), the interscalene brachial plexus is located between the anterior and middle scalene muscles (Fig. 4). The brachial plexus is located 1–2 cm deep to the skin.

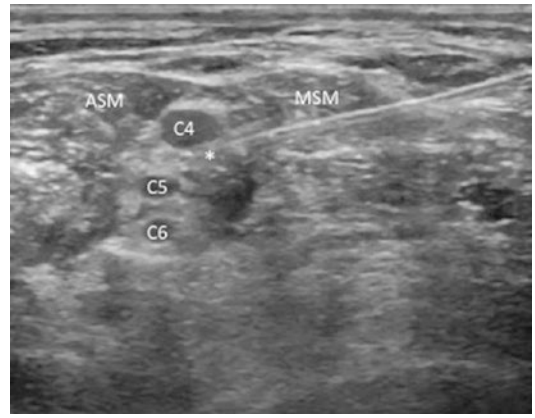


Fig. 4 US-guided interscalene brachial plexus block. Transverse US image shows the in-plane needle tip (*) within the brachial plexus sheath containing the C5, C6, and C7 nerve roots between the anterior scalene muscle (ASM) and middle scalene muscle (MSM). Lateral approach avoids damage to the phrenic nerve, which passes over the ASM

Risks and tips: Blocks of the brachial plexus should be used judiciously as they will produce paresis and loss of function of the arm. Risks include accidental phrenic nerve block (hemidiaphragmatic weakness/paralysis) and cervical sympathetic plexus block (Horner's syndrome). Lateral approach avoids the phrenic nerve, which courses over the anterior scalene muscle (Fig. 4). Controlling injection volume or ablation zone avoid spill into the cervical sympathetic chain. Use of US Doppler and aspiration are vital to avoid intravascular injection. Injection into the brachial plexus should be of low resistance.

5.4 Pelvis and Lower Extremity

Sensory innervation of the hip is divided into anterior and posterior components (Birnbaum et al. 1997):

- Anteromedial: Anterior division of the obturator nerve
- Anterolateral: Nerve to the rectus femoris from the femoral nerve
- Posterolateral: Superior gluteal nerve
- Posterosuperior: Sciatic nerve
- Posteroinferior: Nerve to the quadratus femoris from the sacral plexus

Nerve target: Obturator nerve.

Anatomy: After exiting the obturator canal, the obturator nerve (common obturator nerve) runs in the fascial plane between the pectineus and obturator externus muscles. The anterior division runs between the pectineus and adductor brevis muscles, while the posterior division runs between the adductor brevis and adductor magnus muscles.

Anesthesia distribution: Hip joint and skin of the medial thigh.

Associated tumors: Primary and secondary pelvic tumors.

Therapeutic options: All.

Image guidance: US.

Position: Supine position with the hip slightly abducted and externally rotated.

Entry site: Groin crease.

Approach: Lateral approach.

Technique: US probe is held in the transverse plane. Locate the femoral vessels then move medially along the groin crease to locate the pectineus, obturator externus, and adductor muscles. Fascial planes are seen as hyperechoic lines on US (Fig. 5). The in-plane needle tip is aimed at the fascial plane between the pectineus and obturator externus muscles for obturator nerve block. For nerve blocks to the anterior and posterior division, the probe is moved a few centimeters caudally and aimed at the respective fascial planes (Fig. 5). The fascia should distend without much resistance.

Risks and tips: Color Doppler is helpful in locating the obturator vessels to avoid intravascular injection.

Nerve target: Femoral nerve.

Anatomy: The femoral nerve travels with the femoral artery and vein in the neurovascular bundle as the most lateral structure.

Anesthesia distribution: Hip joint, anteromedial thigh (via the anterior cutaneous branch), and medial leg and foot (via the saphenous nerve).

Associated tumors: Primary and secondary tumors of the hip or proximal femora.

Therapeutic options: All.

Image guidance: US.

Position: Supine position with the hip slightly abducted and externally rotated.

Entry site: Groin crease.

Approach: Lateral approach.

Technique: US probe is held in the transverse plane. Locate the femoral vessels. The nerve is just lateral to the vessels and seen as a hyperechoic structure (Fig. 6). The needle tip is aimed adjacent to the femoral nerve and therapeutic agent injected adjacent to the nerve.

Nerve target: Genicular nerves.

Anatomy: The knee joint is supplied by 12–13 terminal branches arising from the femoral, obturator, and sciatic nerves with multiple variations (Roberts et al. 2020). The most common nerve targets are the superior medial, inferior medial, and superior lateral genicular nerves (SMGN, IMGN, SLGN, respectively) (Choi et al. 2011), which run alongside their corresponding arteries and enter the joint capsule at the tibiofemoral meta-diaphyseal junctions (Fig. 7).

Anesthesia distribution: SMGN: anterior medial joint capsule. IMGN: Inferior medial joint capsule, tibial periosteum. SLGN: Superior lat-

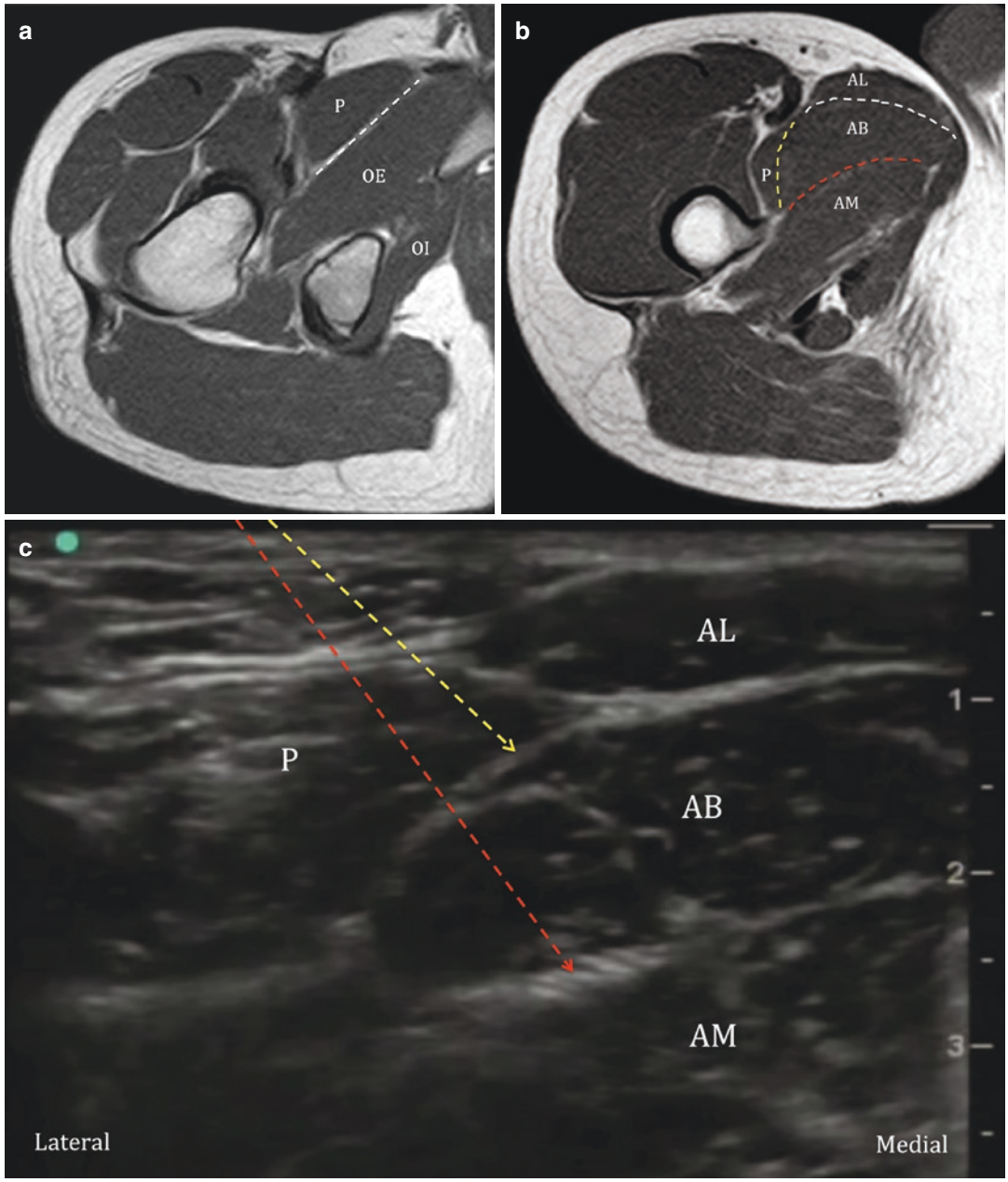


Fig. 5 US-guided obturator nerve block. (**a**) Axial MRI image shows the spatial relationship between the pectineus (P), obturator externus (OE), and obturator internus (OI) muscles. The obturator nerve is located in the fascial plane between the pectineus and obturator externus muscles (white dashed line). (**b**) Axial MRI image more inferiorly shows the spatial relationship between the pectineus (P), adductor longus (AL), adductor brevis (AB), and adductor magnus (AM) muscles. The anterior division of the obturator nerve runs between the pectineus and adductor brevis muscles (yellow dashed line), while the posterior division runs between the adductor brevis and adductor magnus muscles (red dashed line). (**c**) Dashed lines on the transverse US image shows recommended in-plane needle trajectory for anterior division (yellow line) and posterior division (red line) obturator nerve blocks

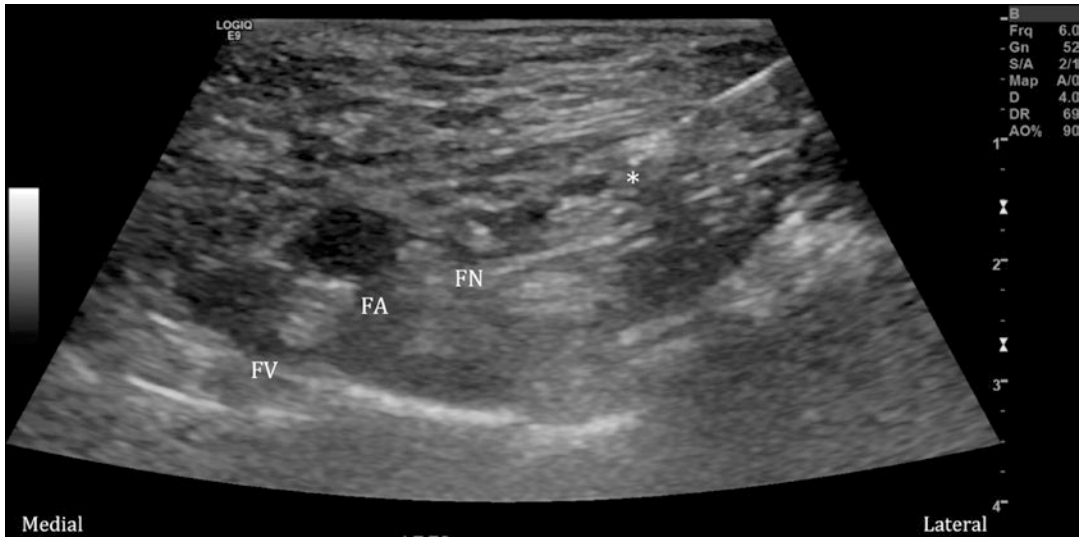


Fig. 6 US-guided femoral nerve block. Transverse US image shows the femoral nerve (FN) as a hyperechoic structure lateral to the femoral artery (FA) and vein (FV). Hypoechoic local anesthetic is seen around the nerve next to the needle tip (*)

eral joint capsule, lateral femoral condyle/epicondyle.

Associated tumors: Primary and secondary tumors involving the knee.

Therapeutic options: All.

Image guidance: US, fluoroscopy, or CT.

Position: Supine with the knee slightly flexed and rotated internally for lateral approach or externally for medial approach.

Entry site: Mid-sagittal plane of the femur or tibia overlying the bony landmarks shown in Fig. 7.

Approach: Medial for SMGN and IMGN block. Lateral for SLGN block.

Technique: For US-guided SLGN block, US probe is placed at the lateral distal femur, held longitudinally in the mid-sagittal plane. Using Doppler mode, locate the superior lateral genicular artery at the junction between the femoral shaft and lateral epicondyle (Fig. 7). Advance the needle in-plane until the tip is adjacent to the genicular artery. Desired agent is injected adjacent to the artery following negative aspiration. The steps are repeated for SMGN and SLGN blocks at the appropriate locations.

6 Associative Therapies

Cement augmentation is another minimally invasive procedure that is complementary to nerve blocks or neurolysis for symptomatic osseous metastasis (Fig. 8). Pain relief stems from consolidation and stabilization of the bone, reducing mechanical pain. Thermal effect from setting of the cement may also contribute to pain relief.

7 Conclusion

Nerve blocks and neurolysis can provide immediate pain relief in terminal patients requiring palliation. Benefits outweigh the trade-offs in the context of end-of-life care. More physicians should consider these procedures in suitable patients.

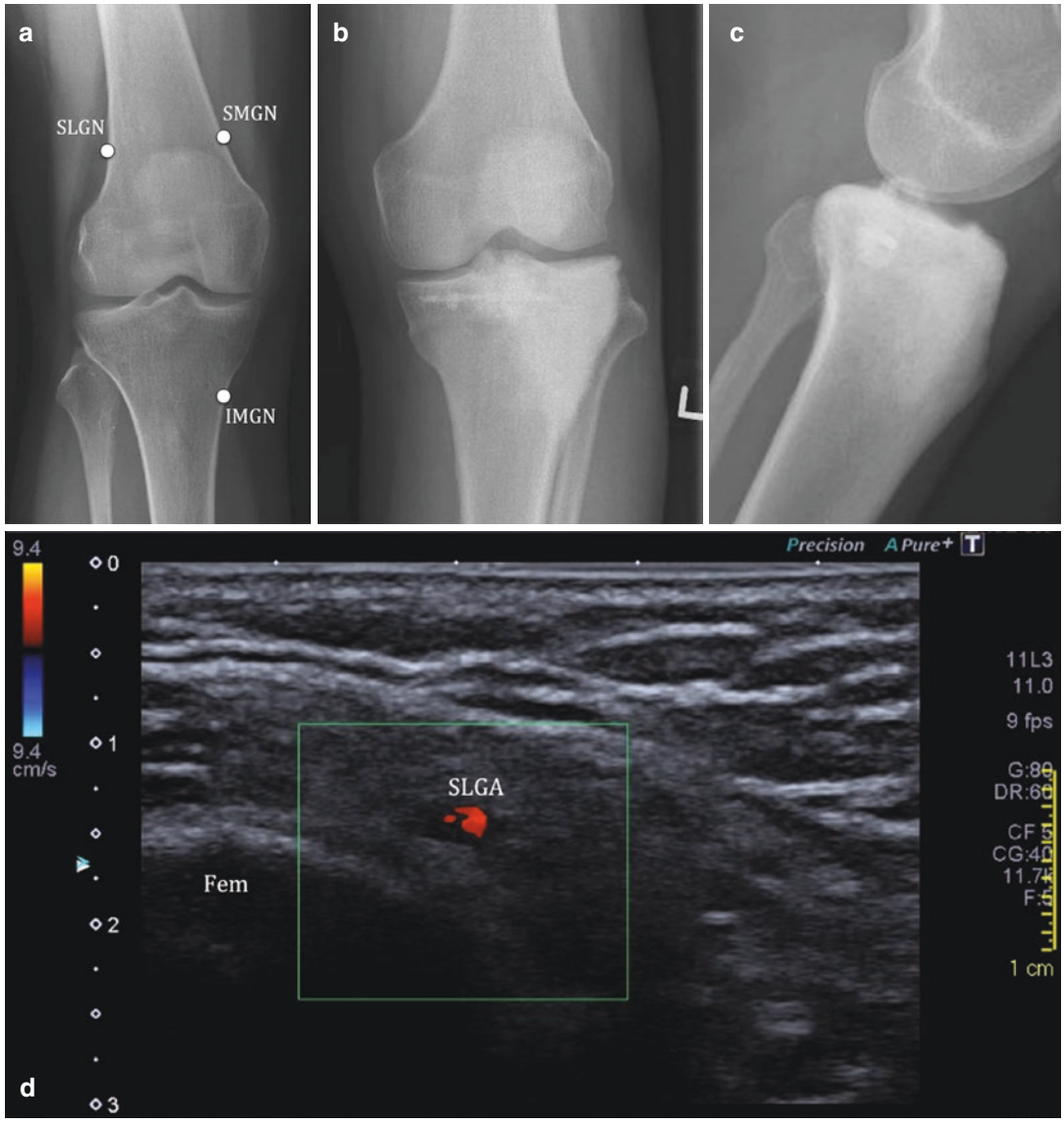
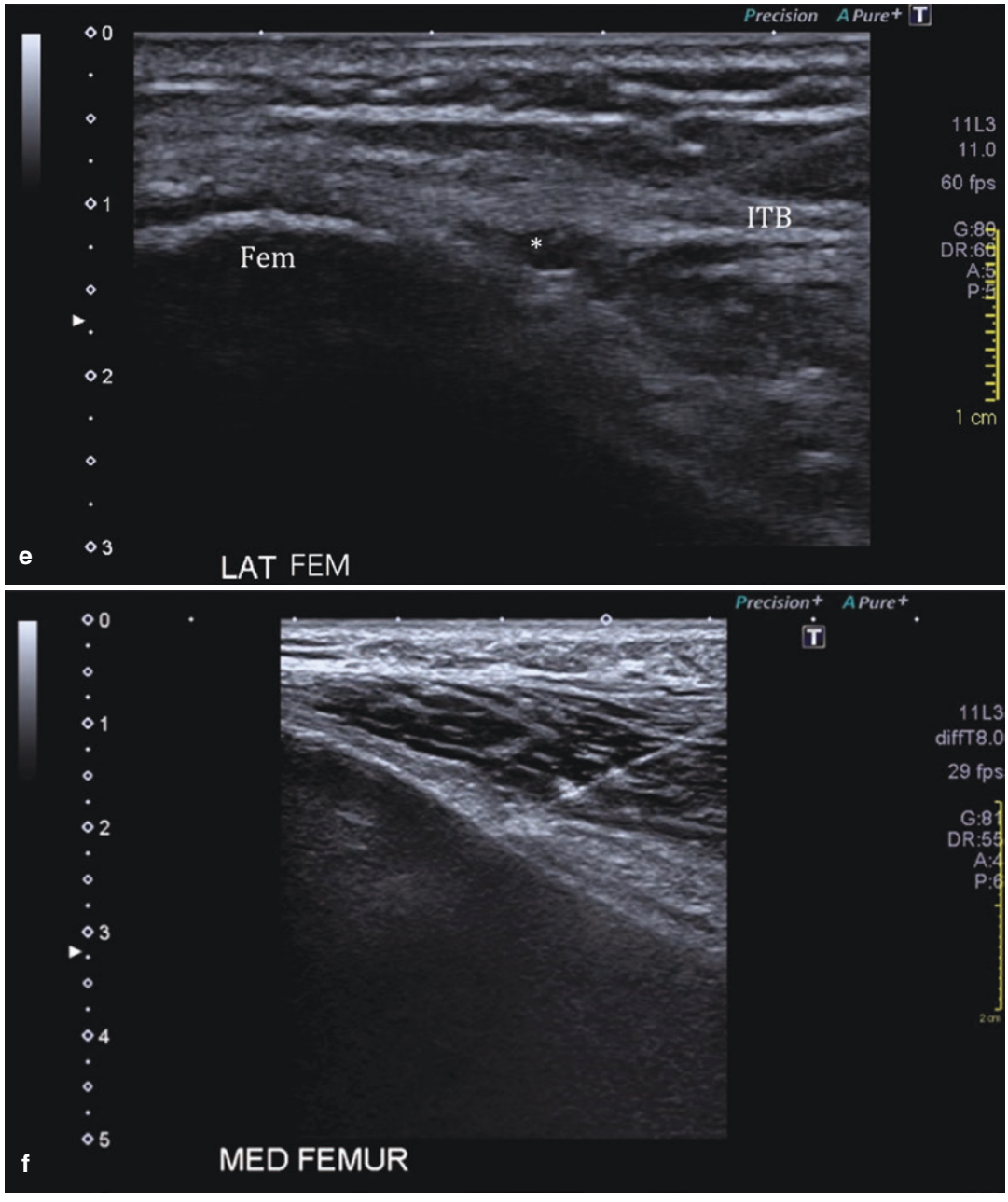


Fig. 7 US-guided genicular nerve block and RFA. (**a**) Frontal radiograph of a normal knee shows bony landmarks for superior medial, inferior medial, and superior lateral genicular nerves (SMGN, IMGN, SLGN) at the meta-diaphyseal junctions of the femur and tibia. (**b**, **c**) Radiographs show osteoblastic metastasis in the left proximal tibia in a patient with metastatic colorectal carcinoma. The patient was treated with US-guided prognostic genicular nerve block followed by RFA. (**d**, **e**) US-guided genicular nerve block. Doppler mode shows the superior lateral genicular artery (SLGA) overlying the junction between the femoral shaft and lateral femoral epicondyle (Fem). The genicular nerve runs adjacent to the corresponding arteries. Bony cortex is seen as a hyperchoic line. B-mode shows needle transversing the iliotibial band (ITB) and small amount of LA at the tip (*) around the SLGN. 1 mL of Bupivacaine 0.5% (5 mg/mL) and 1 mL of dexamethasone (4 mg/mL) was injected around each nerve. (**f**, **g**) US-guided RFA of genicular nerves. Longitudinal US images show RFA probe tip at medial distal femoral meta-diaphysis and proximal tibial meta-diaphysis at the expected locations of the SMGN and IMGN



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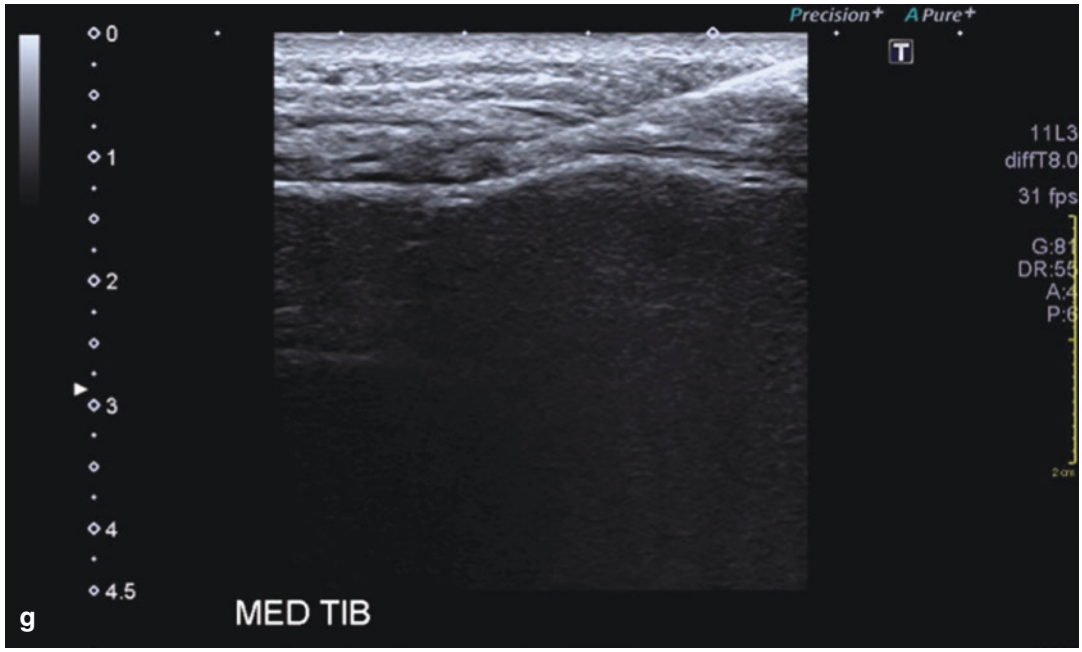

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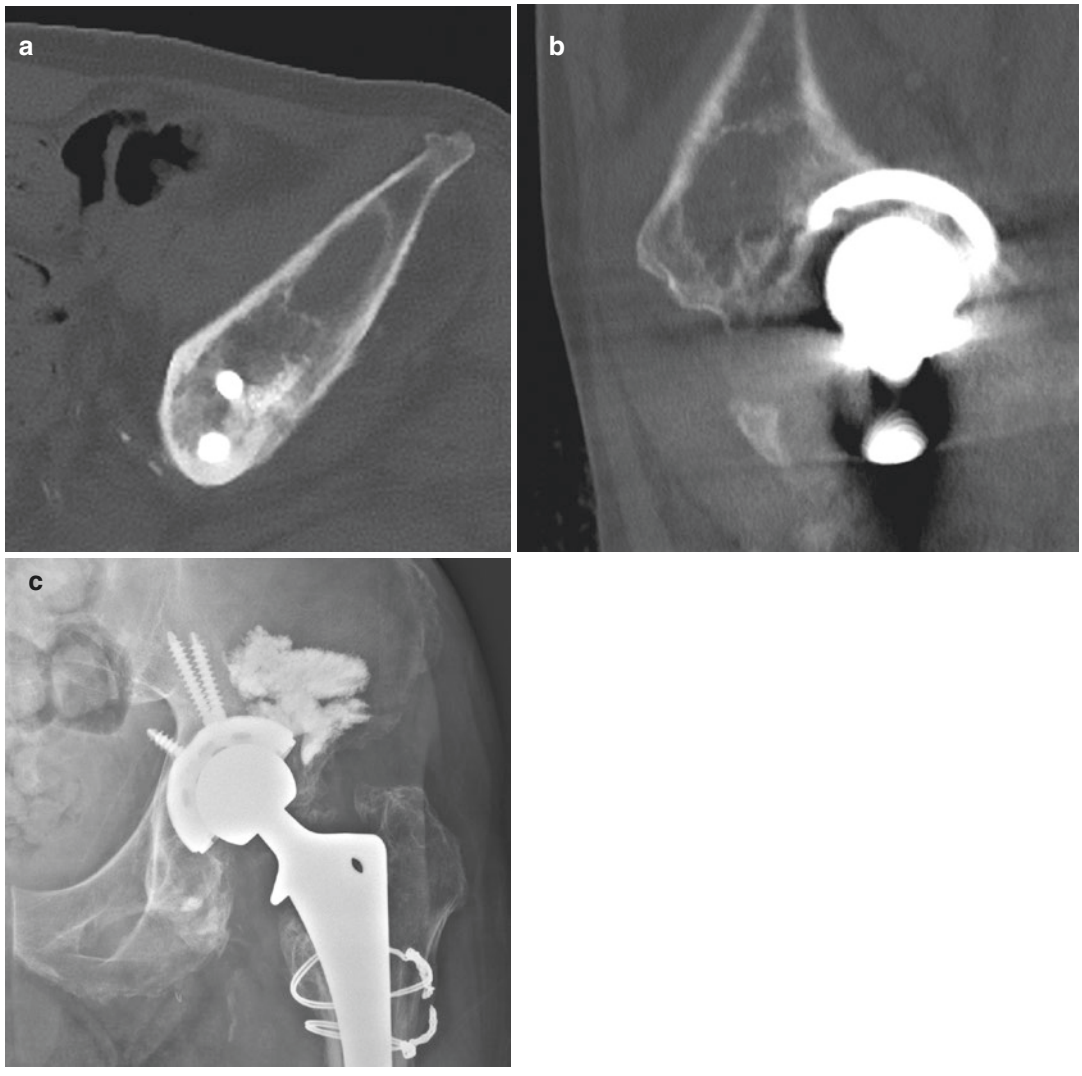

Fig. 8 Cementoplasty following peri-articular nerve block of the left hip. (**a**, **b**) Axial and sagittal CT images show osteolytic metastases in the left acetabulum in a patient with metastatic hepatocellular carcinoma. (**c**) Cementoplasty was performed following nerve block of the peri-articular branches of the left hip

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Autonomic Blocks

Rahul Lohan and Andrzej Krol

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1 Introduction

Pain control is the essence of palliative care. Management of the abdominal pain associated with malignancy is multifactorial and often challenging, necessitating chronic high doses of narcotics, and consequently dealing with their associated adverse effects. An alternate effective way to alleviate the pain associated with abdominal malignancies is to disrupt the nociceptive stimuli originating from the visceral organs, at the level of the various neural plexuses. The fundamentally different terms "block" and "neurolysis" are often used interchangeably. The plexus block involves temporary disruption by means of locally injected steroids and anesthetics, whereas neurolysis aims at permanent obliteration of the plexus by using ethanol or phenol. In this chapter, we describe the anatomy of celiac plexus, superior hypogastric plexus, and the ganglion impar followed by indications, contraindications, techniques, complications, and efficacy of visceral plexus neurolysis.

R. Lohan (✉)
Department of Diagnostic Radiology, Khoo Teck Puat Hospital, Yishun Central, Singapore, Singapore
e-mail: lohan.rahul@ktph.com.sg

A. Krol
Department of Anaesthesia and Chronic Pain Services, St George's University Hospitals, London, UK

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_14

2 Functional Anatomy of Visceral Autonomic Nervous System

The celiac plexus, the largest visceral plexus is located deep in retroperitoneum, over the anterolateral surface of the aorta at the origins of the celiac trunk and the superior mesenteric artery (T12/L1 vertebral level). Its upper border may extend to the aortic hiatus and the lower border to the origin of the renal arteries at L2 level (Kambadakone et al. 2011; Loukas et al. 2010). It comprises of celiac, superior mesenteric, and aorticorenal ganglia; splanchnic nerves from thoracic sympathetic trunk, and abdominal branches of posterior trunk of vagus (Fig. 1). The predominant neuronal input comprises of preganglionic sympathetic efferent fibers through bilateral greater (T5-T9), lesser (T10-T11), and least (T12) splanchnic nerves (Kambadakone et al. 2011; Loukas et al. 2010).

Nociceptive stimuli from the upper abdominal viscera are carried by the special visceral afferent fibers that travel along the splanchnic nerves before terminating in the spinal cord (De Cicco et al. 1997). The celiac plexus supplies sympathetic, parasympathetic, and visceral sensory afferent fibers to the upper abdominal viscera, including the pancreas, liver, biliary tract, gallbladder, spleen, adrenal glands, kidneys, mesentery, foregut, and midgut (up to mid transverse colon) (De Cicco et al. 1997).

The celiac plexus lies in the retroperitoneal space, embedded in the pre-aortic fat, just caudal to the origin of the celiac artery. The stomach and pancreas are anterior to it. Posteriorly, it is separated from the vertebral column by the diaphragmatic crura. The diaphragmatic crura demarcate antecrural celiac plexus from the retrocrural splanchnic nerves. The left celiac ganglion is slightly more caudal than the right, within a centimeter of the celiac artery origin (Kambadakone et al. 2011; Loukas et al. 2010; Titton et al. 2002; Wang et al. 2006). The celiac artery is considered a more reliable landmark for localizing the celiac plexus than the vertebral column. The mean size of the celiac ganglion is about 2.7 cm, ranging anywhere from 0.5 to 4.5 cm (Kambadakone et al. 2011; Loukas et al. 2010; Titton et al. 2002; Wang et al. 2006).

The celiac plexus is often clearly identified at diagnostic multidetector abdominal CT studies (Dal Pozzo et al. 1985; Wang et al. 2010) (Fig. 2). Both ganglia are visualized in 66% of patients, with the left (89%) being seen more often than the right (67%). The right celiac ganglion is seen less often than the left as it is usually confined in a narrow space between the IVC and the right crus of diaphragm. On axial CT images, the ganglia demonstrate a characteristic linear or discoid configuration that resembles the limbs of the adjacent adrenal gland (Wang et al. 2010).

Superior hypogastric plexus is formed by postganglionic fibers from lumbar sympathetic chain, aortic plexus, and parasympathetic fibers from the first two sacral ganglia. It is located between two common iliac arteries, over the anterior surface of the lower third of the L5 vertebral body and upper third of S1 vertebral body (Bosscher 2001; Gunduz and Kenis-Coskun 2017) (Fig. 1). Occasionally, it extends up to L4 and down to S1 vertebral body. It carries nociceptive stimuli form the pelvic organs, i.e., uterus, ovaries, vagina, prostate, and rectum (Gunduz and Kenis-Coskun 2017). Ganglion impar, an unpaired retroperitoneal structure marking the end of both lumbosacral sympathetic chains is the relay center for lower pelvic and perineal pain (e.g., in prostate and colorectal malignancies). This structure lies slightly below the level of the sacrococcygeal joint in pre-coccygeal space (Agarwal-Kozlowski et al. 2009).

3 Celiac Plexus Neurolysis (CPN)

Celiac plexus block refers to temporary disruption of pain transmission via the celiac plexus and is accomplished by injecting corticosteroids or long-acting local anesthetics (Agarwal-Kozlowski et al. 2009; Davies 1993; Lillemoe et al. 1993). The celiac plexus neurolysis, on the other hand, refers to permanent destruction of the celiac plexus with a neurolytic agent such as ethanol. In palliation, the procedure helps in reducing the opioid requirements and their related side effects, and thus improves quality of life in patients with upper abdominal malignancy.

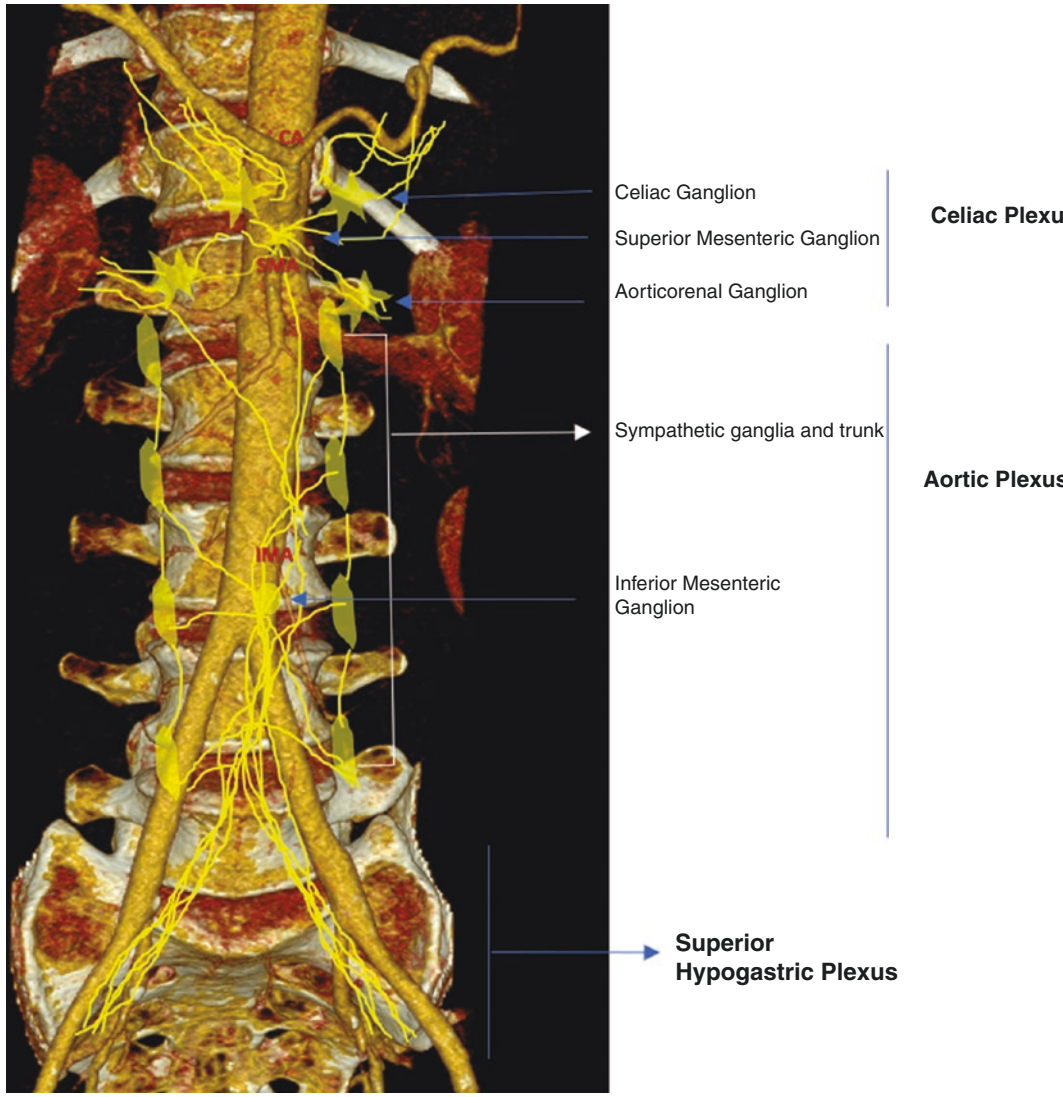

Fig. 1 Schematic using a coronal volume rendered image from an abdominal CT examination demonstrates the location and constituents of celiac plexus, aortic plexus, and the superior hypogastric plexus. *CA* celiac artery, *SMA* superior mesenteric artery, *IMA* inferior mesenteric artery

3.1 Indications

Besides the relief from intractable pain in patients with upper abdominal malignancies, the celiac plexus neurolysis is beneficial in managing severe nausea and vomiting in these patients (Kambadakone et al. 2011). This beneficial effect is attributable to the unopposed parasympathetic activity that arises from sympathetic denervation, resulting in improved gastrointestinal motility. Thus for palliative care, the main indications are

1. Management of intractable abdominal pain caused by pancreatic, gastric, esophageal, or biliary malignancy, as well as metastatic liver cancer and malignancy associated with retroperitoneal lymph node metastasis.

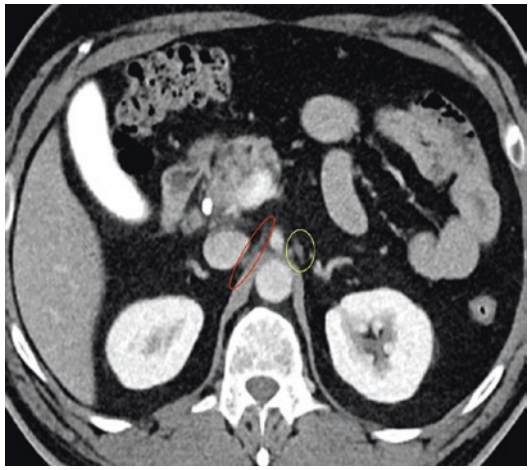

Fig. 2 Axial CT image shows the right (red oval) and left celiac ganglia (yellow oval). The right ganglion is less commonly seen as it occupies a thin linear space between the inferior vena cava and right crus of diaphragm

2. Severe nausea and vomiting not adequately managed by parenteral therapy in patients with upper abdominal malignancy.

The pain associated with upper abdominal malignancies is often multifactorial. For example, pain associated with pancreatic cancer may result from perineural or duodenal invasion, pancreatic or biliary ductal obstruction or spread to the celiac lymph nodes. Somatic pain from cancerous involvement of the peritoneum or abdominal wall is not treated with visceral plexus neurolysis as the somatic pain fibers do not relay into the celiac plexus (Wang et al. 2006). The multifactorial pathogenesis often limits the benefit of celiac plexus neurolysis in alleviating the pain associated with upper abdominal malignancies. Adjunct interventional procedures (such as biliary stenting, direct tumor infiltration) may be performed. This should be appropriately addressed while selecting the patients and communicating with the referring team or caregivers.

3.2 Contraindications

There is no absolute contraindication to celiac plexus neurolysis. Relative contraindications include (Kambadakone et al. 2011; Wang et al. 2006)

1. Severe uncorrectable coagulopathy or thrombocytopenia.
2. Large abdominal aortic aneurysm or an eccentric origin of the celiac artery resulting in no safe trajectory to anterolateral aorta.
3. Intra-abdominal sepsis.
4. Bowel obstruction, due to its effect on gastrointestinal motility.

3.3 Pre-procedural Evaluation

Celiac plexus neurolysis is mainly performed as a palliative treatment in patients hospitalized with advanced cancer. When performed as an outpatient procedure, overnight observation is advised. The patients should fast for at least 6 h and bleeding risk minimized by adjusting the anticoagulants/antiplatelets or administrating blood products as necessary. Celiac plexus neurolysis is usually performed under intravenous conscious sedation with agents such as midazolam and fentanyl. Close monitoring of vital parameters, including electrocardiography, is essential. Oxygen administration may be necessary in older or obese patients.

Prior cross-sectional images must be reviewed in detail to determine the patient position, imaging modality to be used, approach, needle entry site, needle trajectory, and site of neurolytic agent injection (Titton et al. 2002; Wang et al. 2006). Detailed planning helps in achieving a proper distribution of the neurolytic agent in the intended antecrural space, which is essential for increasing the efficacy of procedure as well decreasing the procedure-related morbidity.

3.4 Technique

3.4.1 Imaging Guidance and Patient Positioning

CT-guided techniques are well described and CT is the main imaging modality utilized by interventional radiologists for performing celiac plexus neurolysis. Percutaneous ultrasound and endoscopic ultrasound-guided procedures are also frequently performed.

For the CT or percutaneous ultrasound-guided procedures, the patient is positioned on the table

in a position allowing for the shortest and least complicated route to the celiac plexus. Appropriate patient positioning not only determines a safe needle course, it also minimizes patient's motion. Several different positions may be used depending on the CT approach and the patient's general condition. The most common positions are prone, lateral decubitus, supine, and oblique. Ultrasound-guided injections are mainly performed in supine position.

3.4.2 Site of Neurolytic Injection

Antecrural space injection is preferred over the retrocrural as it results in direct neurolysis of the celiac plexus (Kambadakone et al. 2011). The retrocrural space neurolysis affects the traversing splanchnic nerve fibers only and is not as effective as the antecrural injection. Under CT guidance, the antecrural space can be targeted via bilateral posterior, anterior, transaortic, and transintervertebral disk approaches. Retrocrural injection is primarily performed through a posterior paravertebral approach.

3.4.3 Various Approaches

3.4.3.1 Paravertebral Posterior Approach

The celiac plexus neurolysis is most commonly performed via a bilateral posterior paravertebral antecrural space injection (Kambadakone et al. 2011). The needles are placed on each side through a posterior paravertebral route in a prone (Fig. 3) or lateral decubitus position. A preliminary abdominal CT is performed to localize the celiac and superior mesenteric arteries; and plan an optimal needle path to the celiac plexus. The axial CT section between the celiac trunk and SMA origins is chosen. The needle entry point is prepped in a sterile fashion and subcutaneously infiltrated with 1% lidocaine. Following administration of local anesthetic, a 20–24G needle (such as Chiba biopsy needle; Cook, Bloomington, Ind) is advanced alongside the vertebral bodies into the antecrural space. The needle tip should be approximately 1–2 cm anterior to the aorta, in the space between the diaphragmatic crura and the pancreas; at the level midway between the origins of celiac and superior mesenteric arteries

Fig. 3 Posterior paravertebral approach. The needle trajectories (yellow arrows) and expected distribution of the neurolytics following posterior paravertebral antecrural approach for celiac plexus neurolysis

(Fig. 3). After confirming the needle tip position on CT, the needle is aspirated to make sure that there is no blood return. Dilute contrast (1:50) is injected to further ascertain the correct positioning of needle tip in the antecrural space. The contrast should uniformly diffuse in the retroperitoneal space. Following the free diffusion of contrast, 20 mL of neurolytic is injected on either side.

A mixture of absolute ethanol (95–100%), bupivacaine, and contrast material, in a ratio of 6:3:1, is commonly used (Kambadakone et al. 2011). Ethanol (95–100%) alone may be injected after confirming the needle position with diluted contrast material (Titton et al. 2002). The very low attenuation of ethanol (similar to that of air) makes its distribution easily recognizable on CT even in the absence of contrast material. The other neurolytic agent that can be used is phenol. A diffuse spread of the neurolytic agent on post-injection scanning is an important indicator of adequate destruction of the celiac plexus and should be documented.

3.4.3.2 Anterior Approach

In the anterior approach, the needle is inserted through the anterior abdominal wall and into the antecrural space. The needle tip should be placed anterior to the aorta and the diaphragmatic crura

between the origins of the celiac axis and the SMA. Two needles, with one on each side of the celiac trunk, are positioned. The anterior approach is simple to perform and places the patient in a more comfortable supine position. It is the preferred position when the neurolysis is performed under ultrasound guidance. A preliminary sonographic examination is performed to familiarize with patient's anatomy. The celiac trunk and SMA origins are identified. Both transverse and longitudinal probe positioning are used to plan a safe needle trajectory that would lead to needle tip in between the two vessels (Fig. 4). A long 21–24G needle is advanced under direct sonographic visualization and 30–50 mL of neurolytic agent is administered. 10 mL of 1–2% lignocaine with adrenaline is usually administered to anesthetize the plexus prior to instilling neurolytic solution.

During an anterior approach, it is prudent to find a safe percutaneous path to the celiac plexus without traversing the viscera. However, it is not uncommon that despite exploring all viable options, it becomes necessary to pass the needle through an abdominal organ. The most commonly traversed organs are the stomach and liver, which are often safe in most circumstances, without undue complications. Small bowel loops may be traversed without complications. However, it is important to avoid traversing colonic loop. When advancing needle through liver or kidneys, shortest path should be chosen with least possible

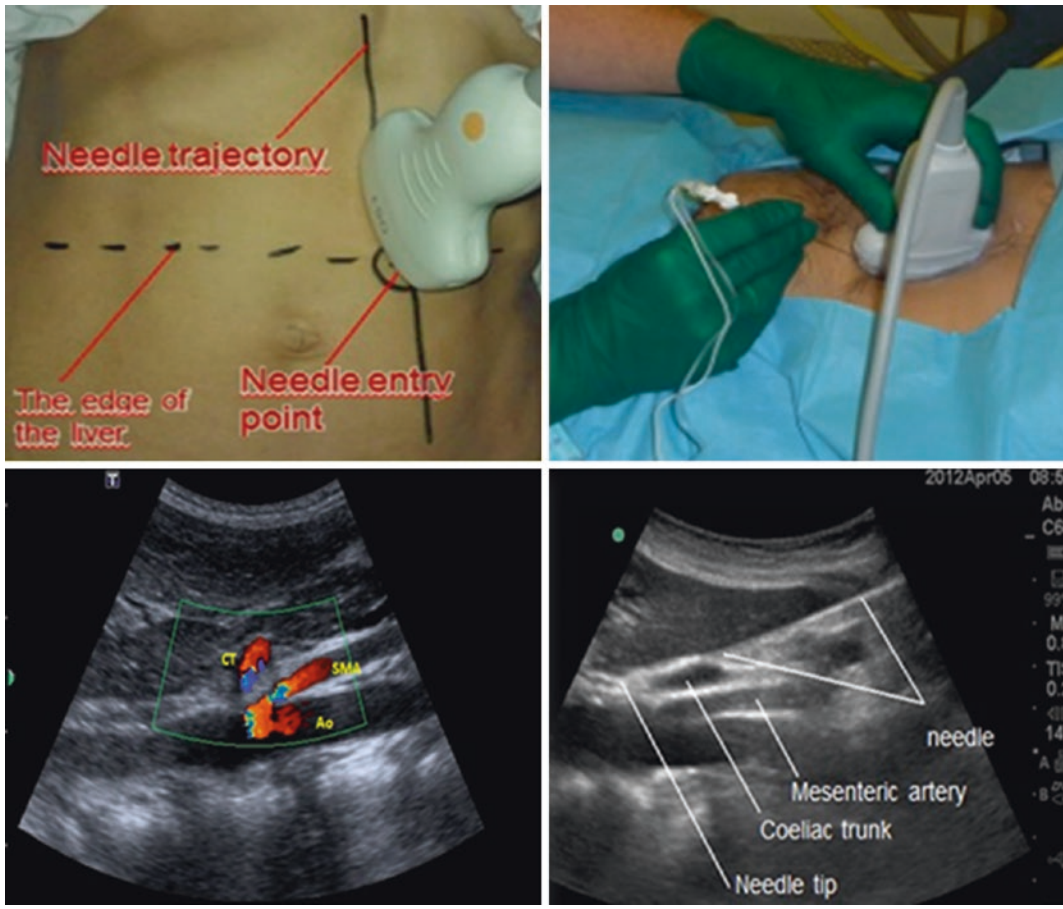

Fig. 4 Anterior ultrasound-guided celiac plexus neurolysis. The probe is positioned longitudinally and the origins of the celiac trunk (CT) and superior mesenteric artery (SMA) are localized. The needle is aligned along the probe axis and advanced under real-time sonographic visualization between the two vessels

punctures through the liver/renal capsule. It is essential to ensure that the coagulation parameters are normal.

3.4.3.3 Other Approaches

Other less frequently used approaches for celiac plexus neurolysis are—transdiscal, transaortic, transcaval, or direct tumor infiltration. In the transintervertebral disk approach, the needle is advanced through the intervertebral disk space lateral to the spinal cord. In the posterior transaortic approach, a fine needle is passed through the posterior and anterior walls of the aorta via a left posterior paravertebral route. With the use of fine needles, this seemingly dangerous route is relatively safe (Kambadakone et al. 2011). Similar to transaortic approach needle can be advanced through and through the inferior vena cava (transcaval) following a right paravertebral route. When the tumor burden in large and the pancreatic tumor or lymphadenopathy has completely occupied the retroperitoneal space, the localization of the celiac plexus becomes almost impossible. In such cases, direct infiltration of the tumor may be attempted for pain control.

3.5 Superior Hypogastric Plexus Neurolysis (SHPN)

3.5.1 Functional Anatomy

Superior hypogastric plexus is formed by postganglionic fibers from lumbar sympathetic chain, aortic plexus, and parasympathetic fibers from the first two sacral ganglia. It is located between the common iliac arteries and lies over the anterior surface of the lower third of the L5 vertebral body and upper third of S1 vertebral body. Occasionally, it extends cranially to L4 and caudad to S1 vertebral body. Afferent pain fibers innervating pelvic organs travel along the sympathetic nerves that originate from superior hypogastric plexus. Therefore, the sympathetic chain disruption by injecting neurolytics at this level treats the pelvic cancer pain (Gunduz and Kenis-Coskun 2017).

3.5.2 Technique

The SHB can be attempted under fluoroscopy, CT, or ultrasound guidance. The aim of the procedure is to position the needle tip at the anterolateral aspect of the L5 vertebra. Similar to CPB, the most commonly used neurolytic is ethanol (Gunduz and Kenis-Coskun 2017).

In the classic fluoroscopic approach, the patient lies prone on the table with a pillow underneath the iliac crest (de Leon-Casasola et al. 1993). The skin entry site is marked at 5–7 cm lateral from the midline on both sides at the L4-L5 disc space level. The skin and subcutaneous tissues were infiltrated with local anesthetic (lidocaine 2%). A 15-cm, 20–24 G needle (Chiba needle) is directed approximately 30–45° anteromedially and inferiorly to miss the transverse process of L5 and the sacral ala (Fig. 5). In the AP view, the needle tip should reach no more than 1 cm medial to the margins of L5-S1. In the lateral view, the needle tip needs to be at the anterior junction of L5-S1. A give away sensation is felt indicating that the needle has traversed the psoas muscle and is in the retroperitoneal space. The contrast (Omnipaque 300) should be contained within the lateral bony edge, anterior to the psoas muscle, and above the sacral nerve roots. After satisfactory spread of the contrast, 8–10 mL of neurolytic solution is injected. Transdiscal approaches are also described which can be done under fluoroscopic or CT guidance.

The common technical problem in fluoroscopic-guided approaches is to bypass the transverse process of L5 and avoid puncture of the iliac artery and vein. This can be avoided by CT or US guidance. For the ultrasound guidance, the patient lies in prone or lateral position. Anterior approach is also described but it often involves traversing the small bowel loops (Mishra et al. 2013). For the posterior US-guided SHPB, the probe is placed above the iliac crest and angulated to see the vertebral body of L5 (Fig. 6). Needle entry is approximately 10 cm lateral from spinous process of L5. The needle is advanced under direct sonographic visualization to reach the anterior surface of L5 vertebral body. The

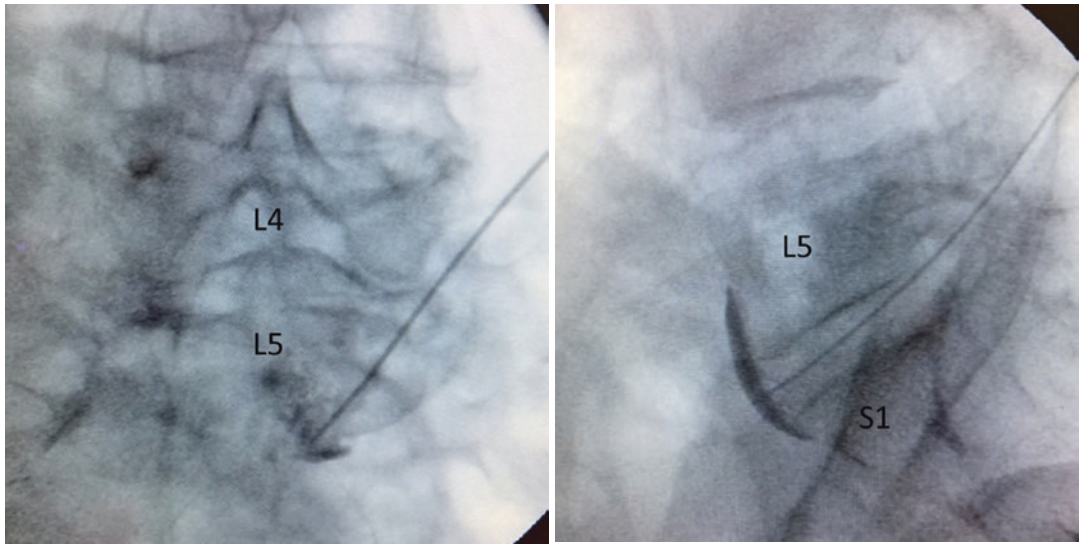

Fig. 5 Fluoroscopic superior hypogastric plexus block. AP and lateral projections demonstrate the needle position and distribution of contrast

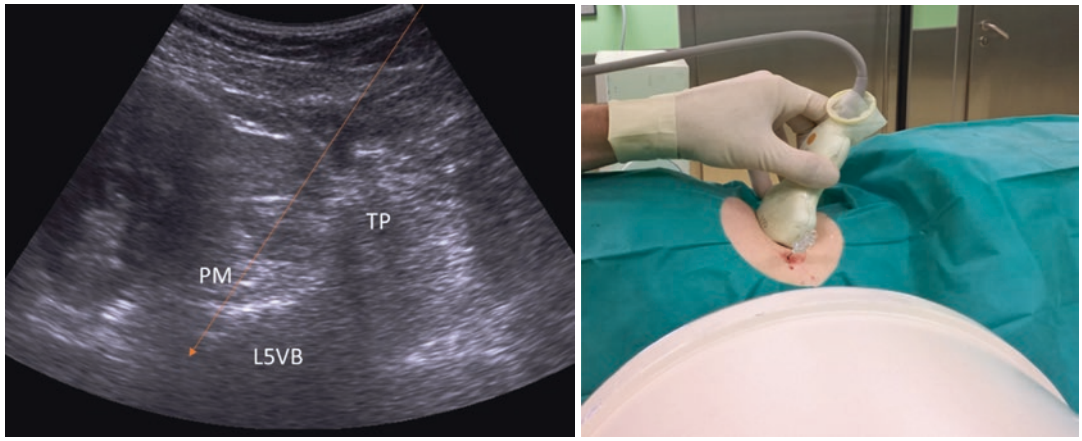

Fig. 6 Ultrasound-guided superior hypogastric block. The patient is lying in a lateral decubitus position. The probe is placed just cranial to the iliac crest and tilted and angled caudally. *PM* psoas muscle, *TP* transverse process, *L5VB* L5 vertebral body. The orange arrow depicts the needle trajectory

needle position is confirmed on fluoroscopy by contrast injection and 10–15 mL of neurolytic solution or anesthetic is administered.

3.5.3 Ganglion Impar Neurolysis (GIN)

The ganglion impar is an unpaired retroperitoneal structure marking the end of lumbosacral sympathetic chains. It lies at or slightly below (up to 2 cm) the level of the sacrococcygeal junction. The indications for blockade or neuroablation of the ganglion impar in palliative care are primarily treatment of pain related to prostate and colorectal malignancies (Agarwal-Kozlowski et al. 2009). Several techniques have been described allowing the ganglion impar to be targeted. These techniques generally utilize fluoroscopic (Fig. 7), CT, or ultrasound guidance.

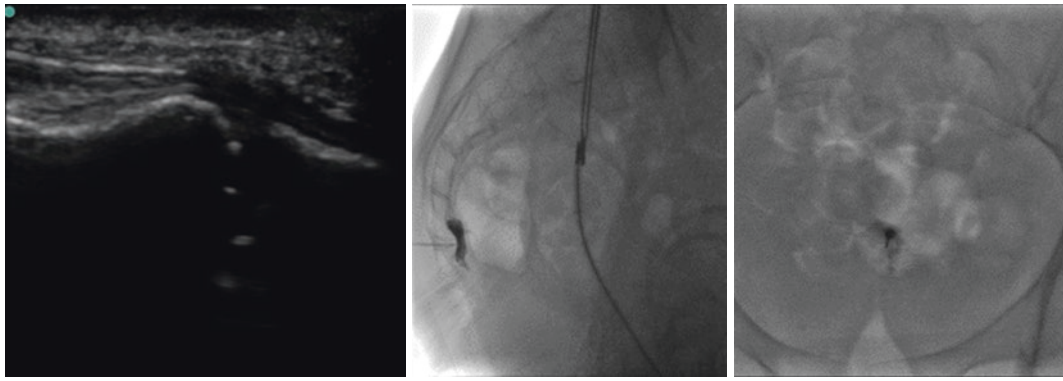

Fig. 7 Ganglion impar block. Ultrasound image in longitudinal orientation demonstrates the sacrococcygeal junction. Lateral and AP projections during fluoroscopic neurolysis of ganglion impar

3.5.4 Post-procedure Care

As the patients undergoing visceral neurolytic therapies are often elderly and frail, these procedures are carried out as inpatient admissions. The patients are admitted overnight for observation and assessment of immediate complications. The patients should undergo bed rest for at least 12 h after the procedure with regular monitoring of blood pressure, heart rate, and other vital signs (Kambadakone et al. 2011). Intravenous fluids are prescribed as needed as orthostatic hypotension may occur post procedure. A focused neurologic examination should be carried out to determine if any neurologic complications are present. The opioids and analgesics are administered as per patients' needs and their dosage recorded. A comprehensive record of the opioids and analgesics dosage helps in determining the efficacy of the procedure.

3.5.5 Complications

Back pain and shoulder pain is common after the CPN and may last up to 72 h. It is likely secondary to the neurolysis affecting the sensory fibers and irritating the diaphragm. Peritoneal irritation may happen with anterior approach resulting in diffuse abdominal pain. Orthostatic hypotension resulting from decreased hypotension may happen in up to 50% of the patients. At least 12 h of complete bed rest and intravenous fluids are advised after the procedure to minimize the risk of hypotension. Transient diarrhea is another common complication (up to 44%) that likely results from unopposed parasympathetic activity. Unopposed parasympathetic activity leads to increased peristalsis and reduced intestinal transit time. Severe complications are summarized in Box 1. Neurologic complications usually result from inadvertent injection of neurolytic agent into the spinal artery or into the subarachnoid space. Most complications are transient and minor when performed with CT guidance and with adequate local anesthetic or intravenous sedation provided before administration of neurolytic solution.

Box 1

Major complications (<2%)

1. Lower extremity paralysis and loss of bladder and bowel function
2. Pneumothorax, arterial injury (e.g., dissection), local hematoma, pleuritis, transient hematuria, pericarditis, intervertebral disk injury, and retroperitoneal abscess

Minor complications

1. Back and shoulder pain
2. Orthostatic hypotension
3. Transient diarrhea
4. Peritoneal irritation

Complications of SHPB and GIB are similarly rare and include—motor, sexual, bladder, and bowel dysfunction, perforation of colon/rectum, sciatic nerve impingement, and infection.

3.5.6 Clinical Efficacy

Celiac plexus neurolysis is primarily indicated for alleviation of intractable pain associated with upper abdominal malignancies, particularly the pancreatic cancer. Its effectiveness in pain control has been recognized since 1992 when the first scientific study showing benefits in patients with pancreatic cancer was published (Ischia et al. 1992). In 2013, a systemic review established its clinical efficacy concluding that CPN should be considered in patients with upper abdominal cancer where the pain is not adequately controlled with systemic analgesics or when significant opioid-induced side effects are present (Mercadante et al. 2015).

Data regarding SHPB and Ganglion impar block in management of cancer-induced visceral pain is limited, in comparison with CPN. One reasonable randomized study of 50 patients with pelvic cancer pain associated with gynecological cancer showed that the patients treated with the block had a decrease in pain intensity and morphine consumption with no statistical differences in adverse effects (Mishra et al. 2013). Large series or randomized trails are lacking and therefore, treatment decision should be determined on case-by-case basis.

3.6 Conclusion

The neurolysis of sympathetic pathways is an effective way of pain control in abdominal malignancies, especially when challenged by serious opioid side effects. Celiac plexus neurolysis is well established as a means of pain control in upper abdominal malignancies and should be considered early in course of palliation. Although not as widely practiced as CPN, SHPN and GIN are useful in certain cases of pelvic malignancies.

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Part IV

Tumour Debulking Solutions

Endovascular Embolisation Techniques

Suresh B Babu, Sivasubramanian Srinivasan, Raymond Chung, Rahul Lohan, and Hsien Khai Tan

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Abstract

Endovascular embolisation is commonly performed across most hospitals which usually requires interventional radiological expertise backed by adequate facilities and a fully trained interventional radiology team. In this chapter, overview of endovascular embolisation techniques is discussed which can be custom tailored to different areas in need, in particular to palliative medicine. Most endovascular embolisation in palliative medicine are done for predominantly either haemorrhage control or mass effect control.

1 Introduction

Endovascular embolisation provides a specialised treatment where the refractory bleeding is controlled or tumours are reduced in size to offer palliation (Niekamp et al. 2017). Most of these

S. B Babu (✉) · S. Srinivasan · R. Chung · R. Lohan
H. K. Tan
Department of Diagnostic Radiology, Khoo Teck Puat Hospital, Yishun Central, Singapore, Singapore
e-mail: Babu.suresh.balasubramanian@ktph.com.sg

© Springer Nature Switzerland AG 2021

P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_15

procedures are done in interventional suite without any need for general anaesthesia. Embolisation can be done with or without moderate sedation. Most of these tumours which present for palliation are usually locally advanced lesions which show invasion into two or three compartments. Mass effect of the tumours or lesions can manifest differently according to the location or aggressiveness. For example, mass effect of brain lesions would be much more pronounced compared to an ovarian tumour in an expandable compartment like abdomen. Aggressive lesion can invade multiple compartments causing nerve damage or other organ damage or compression (Mavrogenis et al. 2013). Tumour angiogenesis is the basis of tumour growth and proliferation with vascular bed promotion from factors like vascular endothelial growth factors (VEGF) and its receptors (Yin et al. 2017). Although endovascular embolisation would not disrupt these factors and receptors, it works on a mechanical level of occluding or reducing the blood supply overall and leads to shrinkage (Goode and Matson 2004). The reduction in volume often leads to relief from reduced compressive symptoms.

2 Indications

Any tumour or lesion can be assessed for vascularity whether it can be suitably embolised (Tan et al. 2015; Niekamp et al. 2017). This is usually seen proximal to the lesion as prominent vascular supply and prominent vascular drainage. Contrast enhancement computed tomography (CECT) or magnetic resonance (MR) imaging would be a useful indicator. CT or MR angiography (images obtained during the arterial phase of contrast study) is very useful in assessing the anatomy of the vessels supplying the tumour (Niekamp et al. 2017). Ultrasonography with Duplex Doppler evaluation also contributes to assess vascularity. Rarely, biopsy of the lesion may be needed to ascertain the histology. Recently, Radiomics, a study to assess the structure of the tumour using images from MR imaging and positron emission tomography (PET), has been used to evaluate the vascularity and metabolic activity of the tumour (Yin et al. 2017).

Careful clinical evaluation of the patient to assess the volume of the tumour is causing the symptoms would be useful before advising of the patients the usefulness of the procedure.

Any part of the body including can be considered for palliative endovascular embolisation of tumour or lesions. Any lesions in the brain or head and neck would need prior training and experience of the operator before embolisation is considered in this region.

3 Contraindications

The usual relative contraindications include bleeding diathesis, renal dysfunction (which precludes contrast usage) active sepsis and poor general outlook, specific contraindications will include large necrotic areas, inability to avoid vital structures or organs and no absent vascular access to the vessel supplying the tumour. Each case should be considered on its own merits and careful evaluation of relevant imaging findings is mandatory before exclusion or inclusion.

4 Techniques

4.1 Access

Most access to any tumour or lesions have been traditionally obtained through right groin. Puncture of common femoral artery is safe and use of vascular closure devices after the procedure reduces the risk of pseudo-aneurysms and bleeding. The vascular access sheaths do not have to be bigger than 6 French (Fr). Recently, radial access has been increasingly used for vascular access.

4.2 Vascular Supply

After access, angiography of the specific region or organ is performed and careful anatomical consideration of vascular supply should be done, which would show the tumour or lesion throughout the arterial phase, tumour or lesion phase and venous phase. Diligent search should also be done for any additional vascular supply.

However, ideally this should have been done from the previously done cross-sectional studies and these help in limiting the volume of iodinated contrast during angiography. Also, angiograms of large areas will be less sensitive and specific to showing exact blood supply, and this will require considerable additional time on the table with setting up of the angiographic pump to evaluate the anatomy as well as in time spent in analysing the images.

4.3 Cannulisation of Target Vessels

Selective cannulisation with a 4Fr or 5Fr catheter to assess the tumour or lesion can be followed by coaxial microcatheter use for embolisation. This coaxial use leads to a safer procedure with high precision. Outer catheter provides stability. Any blockage or failure of inner catheter from any of the embolic agents can be overcome by simply removing it to unblock or to reinsert a new one. Most microcatheters with 2.2Fr or 2.7Fr diameter can be utilised for most embolic agents including low profile coils. Pressure injectors can be used to inject contrast during angiography.

4.4 Embolic Agents

Embolic materials are usually divided into the categories of temporary and permanent (Niekamp et al. 2017). Commonest temporary material is gelfoam and it usually lasts for days. Permanent materials include alcohol, *n*-Butyl cyanoacrylate (NBCA) glue, PVA (Polyvinyl alcohol particles) in graded sizes and coils. Almost always, it is preferable to use permanent agents as the procedure is done for palliation, and there is unlikely a need for late recanalisation. Usually, liquid embolic agents like absolute alcohol or glue and small calibrated PVA particles reach the distal circulation. Larger particles and coils usually causes proximal embolisation which leads to increased risk of tumour recruiting via collaterals which could be quite fast in some tumours or lesions such as arteriovenous malformations (Al-Yamany et al. 2000).

Initial angiogram should be done to evaluate the speed of the flow, volume of the flow and venous return to account for the choice and amount of embolic agents. This is especially important for embolic agents like glue. Any excess volume glue is likely to result in back spill into the proximal supply causing unnecessary collateral damage and loss of function which could be catastrophic in certain areas.

4.5 Phasing of Embolisation

Certain tumours such as renal cell carcinoma can be treated with three-stage embolisation (Maxwell et al. 2007). First, liquid embolic agent like alcohol is very effective in embolising the distal tumour bed. Then this can be backed by particles which would provide embolisation in case of adjustment and loss of distal embolic agent. Proximally, it can be sealed with coil which would control the proximal flow and allows for clotting and lack of flow to distal structures.

Agents like NBCA would provide distal as well as proximal embolisation. However, it needs considerable expertise in using this agent without any complications. (Tips: It is mandatory to use 5% dextrose to flush the catheter as well as to push the glue. Any blood or normal saline will lead to glue solidifying the catheter very quickly. It is also very important to flush the catheter of the glue with 5% dextrose after each usage; otherwise, the catheter will be totally useless due to blockage with glue.)

Choice of coils includes fibred coils and bare coils. Fibred coils provide faster embolisation as clotting is promoted by the fibres. Coils should be carefully chosen for their length and diameter. Catheter compatibility should be checked before opening the coils. Diameter of the coils should be evaluated carefully as any oversizing will lead to lengthening of coil and any under sizing will lead to distal migration. Detachable coils are safer to use compared to pushable coils, as they can be precisely deployed.

Two examples of successful embolisation of advanced tumours are illustrated in the figures (Figs. 1 and 2).

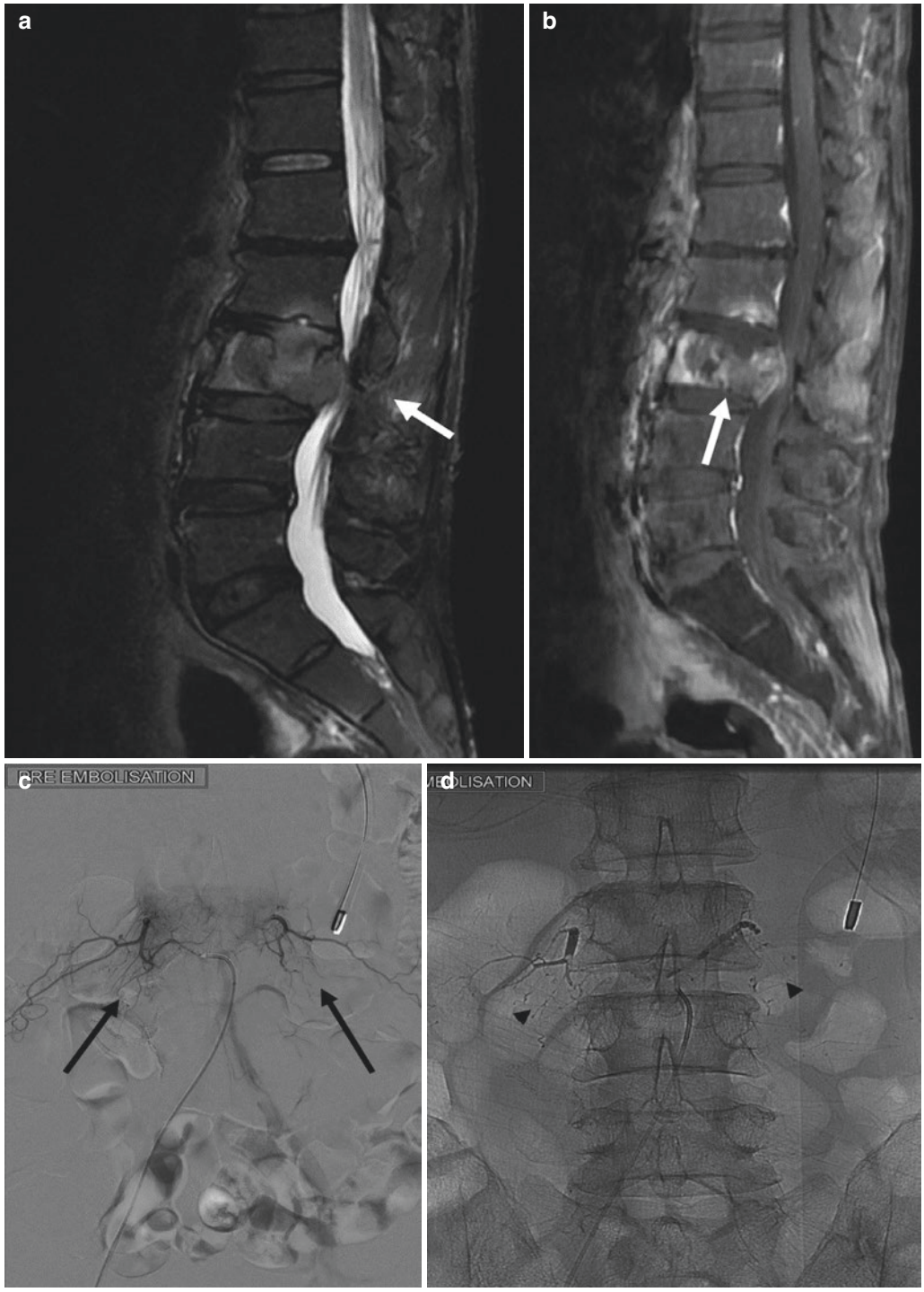
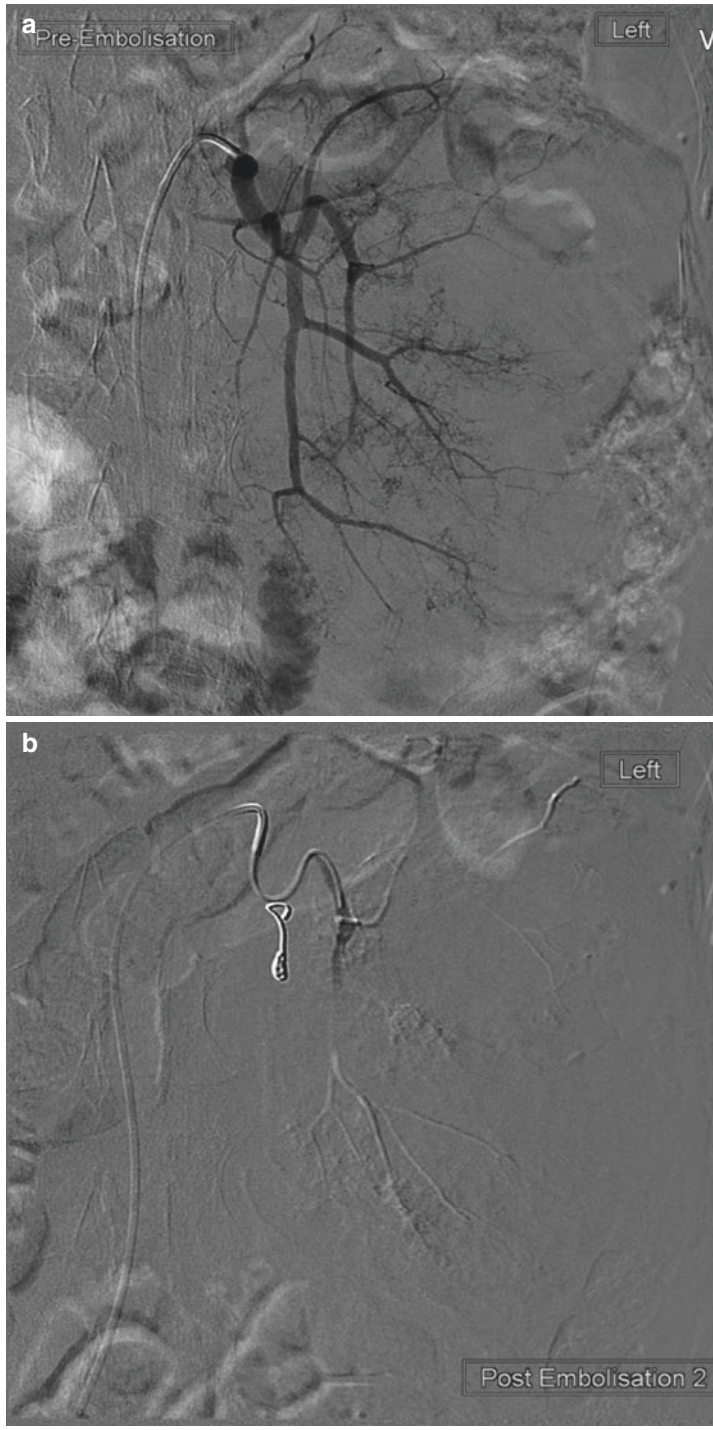


Fig. 1 Patient with a history of multiple (three) primary cancers. Admitted with cauda equina symptoms from compression of expansile vascular metastases of third lumbar vertebra. Treated with palliative embolisation of third lumbar vertebra with significant symptom improvement and patient walked home. (**a**) T2-w sagittal MR imaging showing third lumbar metastases causing compression (white arrows) and (**b**) post-contrast T1-w (sagittal) image showing intense contrast enhancement in keeping with hypervascularity (white arrows) (**c**) Angiogram of lumbar arteries at L3 level showing tumour neovascularity (black arrows) (**d**) Post-embolisation with NBCA glue (arrowheads showing glue cast)



Left renal angiogram showing distorted left renal artery vasculature with tumoural circulation with increased abnormal vascularity throughout

Coaxial catheter system in place after embolising with coils, particles (Contour, 355-500 microns, Boston Scientific) and glue.

Fig. 2 Patient with a massive left renal cell carcinoma with pressure symptoms, with nausea, vomiting and left loin pain. Not suitable for surgical treatment, it was embolised for palliation (**a**) Left renal angiogram showing distorted left renal artery vasculature with tumour neovascularity. (**b**) Coaxial catheter system in place after embolising with coils, particles (PVA particles of 355–500 microns size) and NBCA glue

4.6 Safety Aspects

Proximal balloon occlusion also provides to control the fast flow and static field for embolisation whilst reducing the risk of proximal backflow into the parent arteries. Once adequate embolisation is achieved, a final angiographic run is made to ensure that no collaterals have opened up and that the angiographic embolisation was satisfactory.

5 Associative Therapies

Most of these patients would benefit from conscious sedation; however, most of the patients would have been on analgesics anyway. As such, procedure does not carry the risk of any pain. Careful consideration should be applied to post-embolisation syndrome. Post-embolisation syndrome consists of fever, pain, nausea and vomiting. It is usually self-limiting and should not be mistaken for sepsis. These points should be pointed out clearly in the post-procedural instructions. Post-embolisation syndrome needs symptomatic management such as analgesia and intravenous paracetamol. Most of these patients would not be requiring any antibiotic therapy unless there is evidence of sepsis. If there is evidence of sepsis, cross-sectional imaging (CT) will be useful to rule out any drainable collections.

6 Follow-Up

Patients would require careful monitoring after the procedure. The procedurist should review the patient next day to see the results of embolisation and to rule out any minor or major complications. Treatable complications should be managed proactively. Any renal deterioration from intravenous contrast usage should be managed in conjunction with a nephrologist and intensive care unit. Any renal function worsening of more than 25% increase in creatinine should be considered for temporary renal replacement therapy in the form of haemodialysis or haemofilteration; however, as the patients are only for palliative therapy, careful consideration and thought should be applied before instituting these measures.

7 Conclusion

Endovascular embolisation techniques in palliative care provides safe and quick treatment options with minimal invasiveness whilst the other treatments are either invasive or expensive. Whilst obviating the need for general anaesthesia or major surgery, interventional radiology provides very good symptom control in most palliative group of patients.

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Tumour Ablations

Sivasubramanian Srinivasan

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Abstract

Destruction of tissues by thermal effect or by chemicals is called as ablation. It can be via heating agents by either increasing the temperature (radiofrequency ablation and microwave ablation) or by chemicals (such as ethanol or acetic acid) or with ultrasound (high-frequency ultrasound)/Laser. Although the thermal or chemical ablations were primarily developed for curative management of tumours, it has a role in palliative care as well and studies are still emerging (Callstrom and Charboneau, Tech Vasc Interv Radiol 10:120–131, 2007; Hamamoto et al., BMC Res Notes

S. Srinivasan (✉)
Department of Diagnostic Radiology, Khoo Teck Puat Hospital, Yishun Central, Singapore, Singapore
e-mail: srinivasan.sivasubramanian@ktph.com.sg

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7:765, 2014). Palliative ablation in selected cases of advanced malignancies can be effective when other treatment options such as surgery, radiotherapy, and chemotherapy are not effective or contraindicated.

1 Introduction

The ablation techniques have been primarily developed for curative treatment, for example, thermal ablation of small hepatocellular carcinomas (HCC) and small renal cell carcinomas (less than 3 cm) (McDermott and Gervais 2013; Uhlig et al. 2019). However, they have a role in palliative care. Ablative therapies in selected cases of advanced malignancies can be an option especially to relieve symptoms from the tumour or to debulk the tumour when other modes of treatment such as surgery, radiation therapy, hormonal therapy, or chemotherapy are not effective or contraindicated (McCullough et al. 2011). We shall look into various techniques of ablation, their role in palliative care.

2 Techniques of Ablation

2.1 Radiofrequency Ablation (Pereira et al. 2004)

Radiofrequency ablation (RFA) is based on principle of interaction of tissues with high-frequency alternating electric current. The alternating current causes vibration in the molecules of the tissue. The vibration between the molecules results in friction and loss of energy. The energy gets deposited in the tissues as heat. This heat results in coagulative necrosis of the tissue. The electromagnetic energy source is in the range of 375–500 kHz. The devices may be unipolar or bipolar. The RF ablation circuit consists of cathode (the RF probe) and grounding pads as anode. The electrode tip of the probe concentrates the energy and the grounding pads helps in dissipating the energy.

The aim of RF ablation is that to increase the head gradually from 50 to 90° without causing charring of the tissue which limits the heat transmission and the effect of ablation. The ablation can be enhanced by improving conduction of the heat in the tissue, reducing the tolerance of the tumour, and increasing energy deposition.

The limitation of RFA is that the conductivity depends on the thermal conductivity of the adjacent structures. Thermal conductivity is also limited by vessels (as the flowing blood in the vessels dissipate the heat) causing heat-sink effect.

The types of the RF generators include monopolar or bipolar systems.

2.2 Microwave Ablation (Simon et al. 2005; Brace 2009)

Microwaves are electromagnetic waves in the range of 1–300 GHz. The wavelengths are longer than that of the infrared right and shorter than radio waves. The microwave for ablation is usually between 915 MGz and 2.45 GHz, which is the only range approved for industrial, scientific, and medical purposes. The water molecules exhibit electric dipole movement and create harmonic oscillations in the water molecules, and they try to arrange themselves in line with the alternating current and this results in heat energy. Other molecules are heated by convection. The microwaves, similar to other electromagnetic waves, are reflected or refracted at the boundaries of the matter. The parts of microwave ablation (MWA) system include, a generator which produces the electromagnetic waves, power distribution system comprising of coaxial cables and antenna or probe needles. The needle shaft is usually cooled by circulation of chilled saline or carbon dioxide which enables delivery of sustained power for a given duration of time. Advantages of microwave includes ablation of tissues with low conductivity tissues such as aerated lungs (as compared to radiofrequency ablation), less prone for heat-sink effect, faster ablation time and absent need for grounding pad. Multiple applica-

tors can be placed to increase the ablation zone. Disadvantages of microwave includes larger ablation zone with collateral damage to adjacent structures, lack of clinical data compared to the radiofrequency ablation.

2.3 Cryo-ablation (Rose and Morris 2015; Erinjeri 2013)

Cryo-ablation denotes destruction of tissue by lowering the temperature. Percutaneous cryo-ablation includes insertion of the cryoprobe (specialized needle with active tip) under imaging guidance, and the needle tip is cooled to temperatures below zero degrees. This rapid cooling causes freezing of the extracellular water and osmosis of water from the intracellular to extracellular space. The intracellular dehydration. This results in damage of the enzymes and destruction of the cell membranes. During thawing, the extracellular fluid tries to enter the cells causing swelling of the cells and bursting of the cells. Similar changes also occur in the vessel wall causing endothelial damage and creates oedema in the extracellular space. Delayed damage to the cells occurs by apoptosis, ischaemia due to thrombosis of the vessels and activation of macrophages and neutrophils.

The equipment consists of cryoprobe and cryo-ablation system. The system uses Joule-Thompson effect and circulates argon which expands and causes cooling of the tip of the probe. The heating during the thaw cycle is by expansion of helium. The depressurized gas exits through the hub of the needle to the atmospheric air. The size of the iceball formed can be controlled by choosing the size of the cryoprobes (usually ranges from 1 to 3 mm).

Advantages of cryo-ablation includes, real-time monitoring of the ablation zone by the ice formation, relatively less painful because of the anaesthetic effect of the ice and the procedure can be done under moderate sedation, cryo-ablation does not affect CT or MRI as no electromagnetic or radiofrequency waves are used for the thermal energy, the structural component of tissue is maintained compared to heat-based ablations.

Disadvantages include cryo shock (hypotension, multi-organ failure, inflammatory mediators induced DIC), bleeding complications (can be more than RFA/microwave ablation). Other disadvantage is the cost involved.

2.4 Other Ablative Therapies

2.4.1 High-Intensity Focused Ultrasound (HIFU)

Ultrasound waves are sound wave with frequency above the audible range for humans (more than 20,000 Hz). The intensity is measured in W/cm. The focused intensity beams of HIFU are usually in the range of 10 W/cm^2, and this results in deposition of high energy which causes heating of the tissue and causes coagulation necrosis. (The diagnostic ultrasound intensity is around 100 W/cm^2.) The high-intensity waves cause elevated temperature (over 60 °C) leading to irreversible cell death through coagulation necrosis (Tempany et al. 2005; Wu et al. 2005; Garnon et al. 2013).

HIFU ablation is currently used to treat various conditions (apart from uterine fibroids) such as benign prostatic hyperplasia, carcinoma prostate, in operable solid organ metastasis, bone metastasis, and breast cancer. The image guidance and monitoring is either by ultrasonography or MRI although MRI is better for monitoring (by MR thermometry) to assess coagulation necrosis.

Prerequisites for HIFU ablation:

1. Skin entry site should be clean.
2. Clear acoustic window (without air/gas/bone interface).
3. Local or regional anaesthesia or conscious sedation to restrict mobility of the patient to improve target ablation.

Limitation of HIFU include time taken for ablation, unpredictable response, complexity of the equipment, and difficulties in monitoring the temperature or area of coagulation necrosis.

2.4.2 Chemical Ablation (Garnon et al. 2013)

The chemicals used for ablation in clinical practice are ethanol and acetic acid. These can be used alone or in combination with thermal ablation techniques. Acetic acid produces larger area of necrosis for same volume of tumour, hence preferred for large tumours, although ethanol is easily available and more widely used. Apart from treatment of primary liver tumour, ethanol is also used to treat painful bone metastasis, adrenal tumours, and neurolysis. Conscious sedation or anaesthesia is necessary for ethanol ablation of tumours as it is a painful procedure. The procedure can be performed under US and fluoroscopic guidance or CT guidance. Initial checking is done by injecting diluted contrast into the mass lesion (non-necrotic part in cases of non-osseous tumour). If there is opacification or leakage of contrast outside the tumour injection of chemical agent cannot be safely performed. The total volume is around 5–25 mL and changing the direction of the lesion or repositioning the patient may be necessary for maximum ablation of the tumour.

Neurolysis or alcohol ablation of nerves is an effective procedure for pain control in patients with malignancies causing neural involvement. The site of injection depends on the malignancy, for example, in pain related to pancreatic cancer coeliac plexus neurolysis can be considered. Procedure is usually performed under local anaesthesia. CT is the best modality for precise positioning of the needle. Usually, 22-G needle is used and is positioned closed to the anatomical location of the neural plexus and 5–10 mL of ethanol is administered. Pain relief is usually immediate after injection.

Limitation of chemical/ethanol ablation are variable response to the treatment, difficulty in controlling the agent, and accurate prediction of the margin of ablation is not possible.

3 Patient Preparation

The decision for ablative therapy is usually taken in a multidisciplinary meeting. The treatment option should also be discussed with the patient and close family members. Informed consent should be obtained after patient understands the procedure, its rationale, potential risks and need for follow-up after the procedure. Anaesthetist review may also be necessary. Antiplatelet medications (such as Aspirin or Clopidogrel) should be stopped 5–7 days before the procedure.

4 Anaesthesia for Ablation (Fox and Harvey 2005)

Ablative therapies need good local or regional or general anaesthesia. Involving an anaesthesiologist for ablation had advantages such as to minimize pain during the procedure and to enable cooperation and safe performance of the procedure. As most patients who require palliative treatment are severely morbid, monitoring vital parametres and maintaining haemodynamic stability is very important and anaesthesiologists can be of immense help during the procedure.

Ablation can be performed under conscious sedation, monitored anaesthesia care, regional anaesthesia, or general anaesthesia. For conscious sedation, short-acting benzodiazepines (such as Midazolam) and opioids (such as Fentanyl) because of their quick onset and short action and the ability to be reversed. Airway protection and oxygen supplementation may be required in very sick patients. Monitored anaesthesia care involves deeper level of sedation. Regional anaesthesia involves neural blockage of particular region where anaesthesia is required. For example, intercostal nerve blocks, brachial plexus block, celiac plexus block, and epidural anaesthesia. Significant number of patients undergo general anaesthesia. The airway is secured by endotracheal tube or laryngeal mask.

5 Various Regions

5.1 Chest

Thermal ablation of primary or secondary lung tumours is relatively new and considered with either curative intent of small tumours or for pain

alleviation or debulking of large lesions in a palliative care setting. Palliative ablation is used in stage 3 and stage 4 lung cancers. It can be combined with other treatment options such as radiotherapy and chemotherapy (Roy-Choudhury 2013).

Radiofrequency ablation is the most common type of ablation performed although there are advantages of microwave ablation and cryotherapy includes better ablation when the lesion is close to bronchus or large vessel.

Special precautions before ablation of lung lesions:

- Routine pre-procedural care, respiratory function tests especially FEV1.
- Staging CT/PET.
- Pre-operative biopsy findings (especially in primary lung tumours).

Contraindications include pneumonectomy on the opposite side or diseased lung, FEV1 < 0.8, very close to large bronchus or major blood vessel or heart. The presence of pacemakers is also a relative contraindication.

5.1.1 Procedure

Air around the lesion limits the conduction of heat. Hence, the ablation is usually confined to the tumour. However, if the tumour has infiltrative margins, then the ablation especially with RFA may be inadequate. In such cases, microwave or cryo-ablation are superior. Cryotherapy also provides theoretical advantage of reduced freeze-thaw cycle as the alveoli surrounding the tumour are filled with fluid. Cryotherapy is also relatively safe in tumours which are close to mediastinal structures. However, tumours within 1 cm of the mediastinal structures are not treated. If a tumour is close to a large pulmonary vessel, then cryotherapy or microwave are preferred (to reduce the possibility of heat-sink effect which is common with RFA). Fissures are usually avoided to reduce the risk of pneumothorax. Care has to be taken when treating tumours close to major bronchus as there is a risk of broncho-pleural fistula.

The procedure is usually performed under CT guidance, under monitored sedation, or general anaesthesia. Anaesthesia is preferred if the lesion is close to pleura. Long airway tube may be necessary as the patient may be moved in and out of the CT gantry multiple times. Adequate padding for the pressure points may be needed as the patient will be placed in prone position. Antibiotics are given before the procedure. Shortest trajectory is usually preferred and large blood vessels, bronchi should be avoided.

5.2 Liver

Image-guided ablation is considered as the non-surgical choice of treatment for early hepatocellular carcinomas less than 3 cm. However recently, ablation has been performed in larger tumours and in combination with TACE. Ablation of liver tumours is an established technique and the benefit is well proven. Percutaneous ethanol injection, RFA and MWA are commonly used. Patients with cirrhosis should be of Child-Pugh class A or B. Metastatic lesions (up to three lesions) less than 3 cm are also amenable for thermal ablation (Solbiati et al. 2005). Absolute contraindications include Child-Pugh class C cirrhosis, difficult access, active infection, and significant extra-hepatic disease (Soulen and Kernagis 2005; Galanakis et al. 2018; Winokur and Brown 2013).

Percutaneous ethanol injection is performed with ultrasound guidance. Multi-sidehole needles or multiple end-hole needles (20–23G size needles) placed within the tumour and 95% ethanol is injected slowly. A total volume of 2–8 cm^3 is injected in a single sitting.

RFA or MWA is performed with US or CT guidance (or rarely under MRI guidance), under conscious sedation, or general anaesthesia. Hydrodissection with 5% dextrose should be performed through a 20–22G needle to displace structures or to avoid heating of vital structures such as gall bladder if the tumour is in close proximity to these structures. The target temperature for RFA is around 55–100 °C. The ablation should extend to around 1 cm margin outside the tumour. Better results are achieved with cirrhotic livers (with HCC) compared to metastasis because of

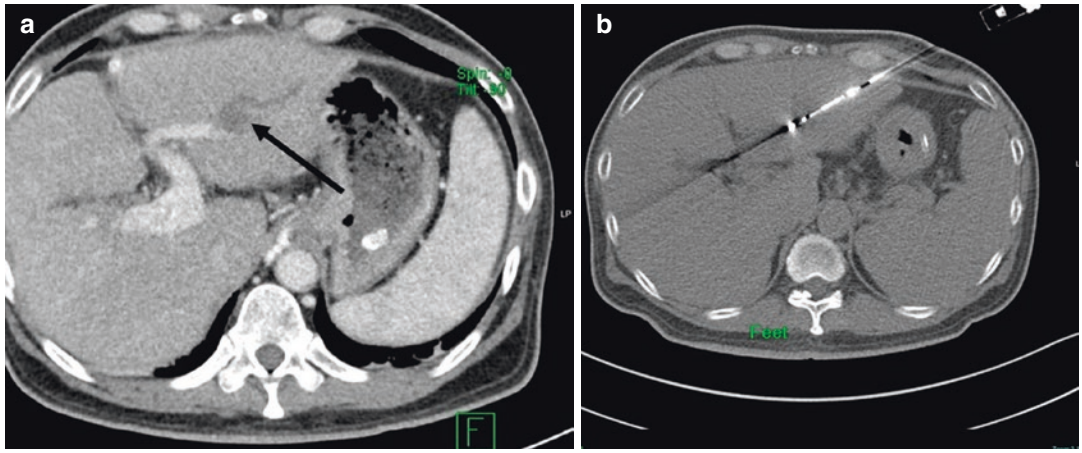

Fig. 1 (**a**) Axial contrast-enhanced CT (portal venous phase) showing an HCC. (**b**) Microwave ablation (MWA) was performed under CT guidance

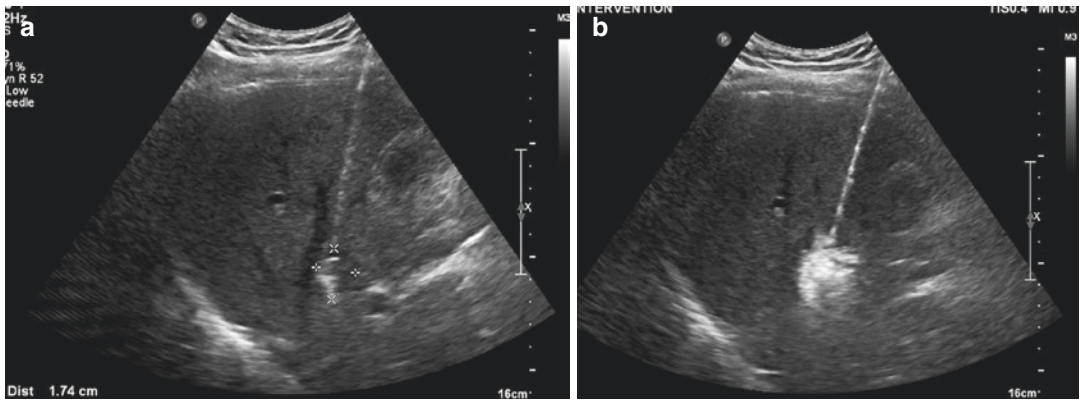

Fig. 2 (**a**) Oblique longitudinal US scan showing an HCC with RFA probe placed under US guidance. (**b**) Echogenicity with dirty shadowing due to air bubbles during thermal ablation

insulating effect of the cirrhotic liver ("oven effect"). MW ablation is less susceptible to heat-sink effect and higher temperatures are achieved with larger ablation zones (Figs. 1 and 2).

The outcome is dependent on the size of the tumour and degree of cirrhosis. 5-year-survival results following percutaneous ethanol injection in patients with Child-Pugh class A patients is around 41–60% and for RF ablation it is around 43–64% for Child A cirrhosis and 31–38% for Child B cirrhosis (Shibata et al. 2002). MWA has similar rates but data is limited. In one series, cases of metastasis from colorectal tumours, local control was obtained in 78% of patients with small tumours <2.5 cm (Solbiati et al. 2001). Limited data is available in patients with metastasis from other tumours. Morbidity and mortality in patients with hepatic metastasis is variable as these patients have significant morbidity from the neoplastic disease and comorbidities.

5.3 Adrenal

Image-guided ablation in adrenal tumours is indicated in patients who are not fit for surgery due to comorbid conditions. Adrenal ablation has been performed in patients with primary adrenal tumours especially nonfunctioning adenomas or functioning adenomas, adrenocortical

carcinoma, pheochromocytoma and metastasis from renal cell carcinoma, melanoma, lung and gastro-intestinal tumours (Beland and Mayo-Smith 2009; Uppot and Gervais 2013).

The management options should be decided in a multidisciplinary tumour board. Pre-procedural clinical evaluation should be performed and all the imaging studies should be reviewed. Laboratory tests should be evaluated for baseline or pre-treatment values of hormones in functioning adrenal tumours.

Pre-procedural biopsy of the adrenal tumours is usually performed few weeks before the procedure. The biopsy procedure also serves as a guide for planning the trajectory and patient positioning. Image-guided biopsy should be carefully performed especially in functioning neoplasms (such as pheochromocytoma).

Endocrinological consultation is useful prior to the procedure as alpha-blocker may be initiated for the patient (with titration with beta-blocker). The procedure is ideally performed under general anaesthesia, under an experienced anaesthesiologist who will be needed to be prepared for management of hypertensive crisis.

Ablation is usually performed with CT guidance in decubitus or prone position. Safe trajectory has to be chosen from the pre-procedural contrast-enhanced CT avoiding pleura, adjacent viscera, and vessels. If direct access is not available trans-hepatic access may be used.

RFA is the most commonly employed technique for ablation of the adrenal tumours. Two of the early series reported good results with ablation of adrenal tumours. In the series reported in 2003 by Wood et al., 15 unresectable tumours in 8 patients with primary and metastatic adrenocortical carcinomas were included and mean period of follow-up was 18.3 months (maximum of 27 months) (Wood et al. 2003). Local control of the tumour was achieved in 8 out of 15 tumours (especially when the size is less than 5 cm). None of the patients had hypertensive crisis. Another study had 13 lesions in 12 patients and 11 out of them had metastatic lesions to the adrenals. Mean duration of follow-up was 11.2 months and ablation was successful in 11 out of 13 patients (Beland and Mayo-Smith 2009).

Other methods of ablation include microwave ablation, cryo-ablation, and chemical ablation. However, reports and studies are limited.

Complications of ablation of adrenal glands include hypertensive crisis, haemorrhage, pneumothorax, infection, and pain.

The success of ablation is assessed by follow-up imaging which shows reduction in the size and absence of enhancing tumour (in a previously enhancing tumour) and also reduction in the abnormal hormonal levels in patients with functioning tumour.

5.4 Kidneys

Although surgery is the treatment of choice in patients with renal cell carcinoma, ablative therapy is indicated in patients who have small tumours <4 cm and not suitable for surgery due to comorbidities, single kidney, bilateral tumours (such as in patients with Von-Hippel Lindau disease), patient preference and palliation for haematuria (Nakasone et al. 2012; Fotiadis 2013). RFA and cryoablation are the most popular ablative techniques for the treatment of renal tumours (Figs. 3 and 4). However, newer options include MWA, HIFU, and Laser. Sometimes trans-arterial embolization can be combined with ablation.

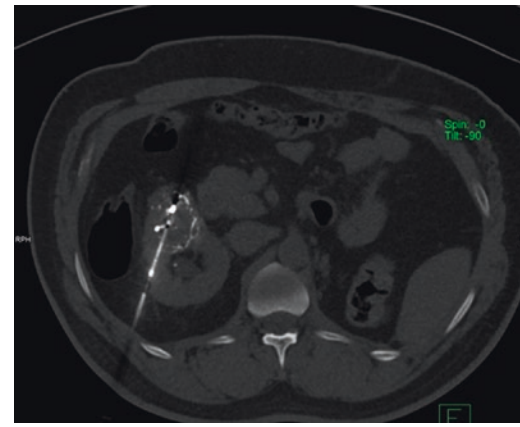

Fig. 3 A 54-year-old man with 5 cm right renal cell carcinoma (RCC). Microwave ablation (MWA) was performed after embolization. There are few dense areas in the tumour as lipiodol was injected to opacify the tumour

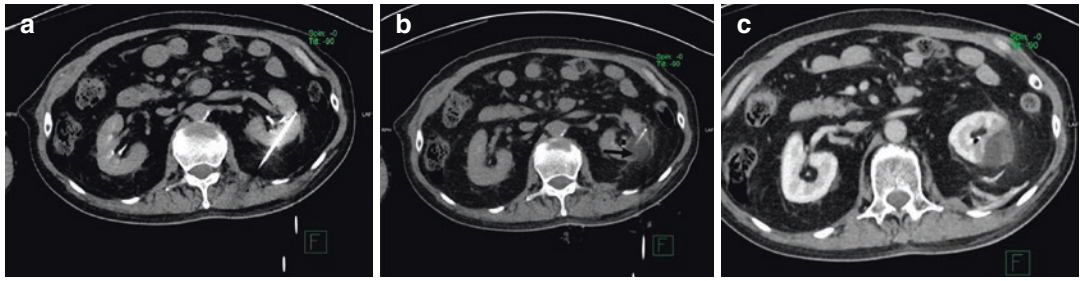

Fig. 4 Cryoablation of left renal tumour (**a**) Axial CECT showing probe within renal tumour. Three probes were used (**b**) during the procedure (iceball formation around the probe) and (**c**) after treatment. The tumour was successfully treated

Specific contraindications include irreversible coagulopathy, extensive metastasis, sepsis, and low life expectancy less than 1 year. As in the case of adrenals, procedure is usually performed under CT guidance with or without the help of US. The procedure may be performed under monitored anaesthesia care or conscious sedation or general anaesthesia. The procedure is performed in prone, semi-prone, or lateral decubitus position. Major structures, pleura, and vessels should be avoided. Hydrodissection (with 5% dextrose) may be helpful to displace structures such as overlying bowel loops. Normal saline is avoided for hydrodissection due to the risk of transmission of current through the ions. If the tumour is close to the collecting system, retrograde pyeloperfusion with cold dextrose 5% through a ureteric catheter should be performed. The ureteric catheter is ideally placed by urologist just before the ablation procedure. The urine catheter is usually removed at the end of the procedure. Biopsy of the lesion can be performed just before the ablation. The ablation zone should include at least 0.5 cm of margin outside the tumour. When cryo-ablation is used, a double freeze-thaw cycle is required. Mean duration for cryo-ablation is around 40 min with first freeze lasting around 8–15 min and second freeze around 5–20 min. Each thaw cycle would last around 10 min. The major complications of renal ablation includes bleeding, injury to collecting systems, post-procedure follow-up should be performed as per institution protocol and successful ablation is considered when there is reduction in the size of tumour (in large tumours) and the absence of enhancing tumours (in small tumours).

5.5 Prostate

Indications for ablation of prostate includes prostatic carcinoma confined to the organ, volume <40–50 mL, PSA level <20 ng/dL. Contraindications include high PSA value >20 ng/dL and Gleason score >7. (Relative contraindications include history of previous surgeries such as transurethral resection, gland volume >50 cm^3, and coagulopathy.)

Cryo-ablation is the choice for ablation of prostate tumour, under US or MR guidance (transrectal or transperitoneal probe). Two 10-min freezing cycles separated by a 10-min thawing cycle are usually performed. Follow-up is usually performed by MRI, clinical examination and PSA levels up to 3 years. Study by Long et al. shows that success rate is more than 60–75% when followed up at 24 months (Long et al. 2001).

5.6 Primary Bone and Soft Tissue Tumours

Traditionally, reduction of the tumour volume is achieved by radiotherapy, debulking surgery, and chemotherapy. However, these have limitations. Surgery has increased risks of bleeding and other complications. Symptomatic relief with radiotherapy is not immediate, and radiation has multiple side effects if the dose of radiation is very high.

Palliative ablation of painful bone or soft tissue tumours have been reported (Fig. 5). RFA is usually used and pain relief is achieved by coagulation necrosis (Hamamoto et al. 2014) and

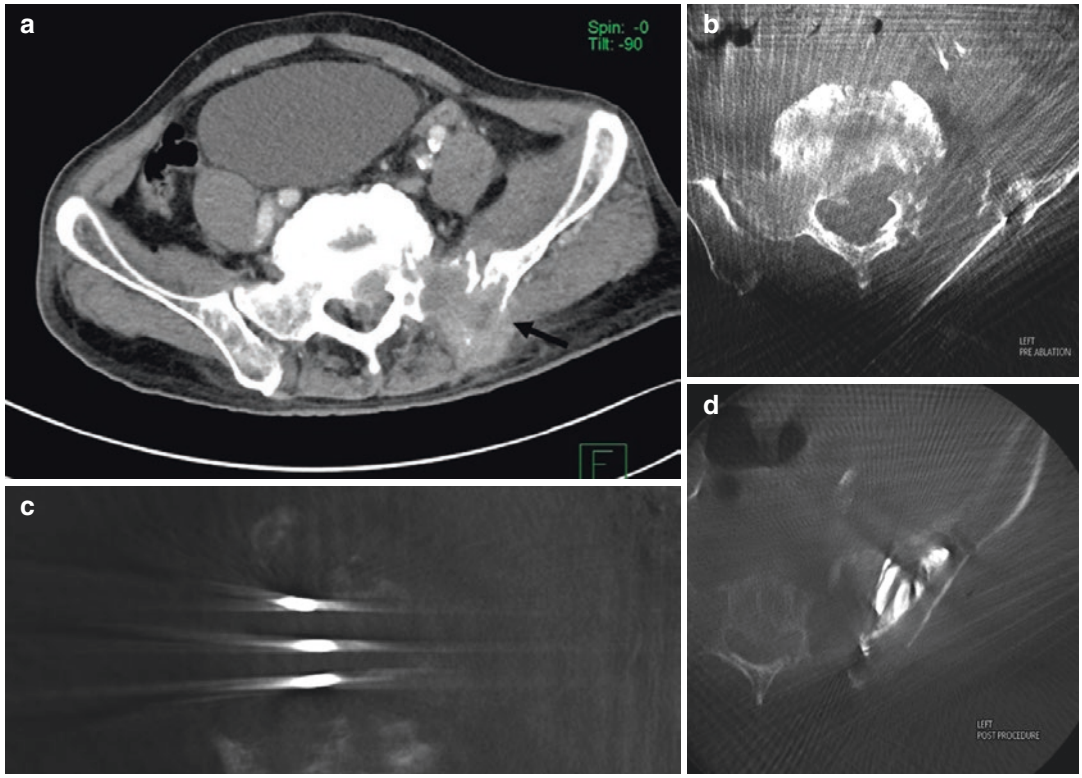

Fig. 5 (**a**) Axial contrast-enhanced CT of a 74-year-old man showing left sacro-iliac metastasis from known lung carcinoma (arrow). (**b**) Radiofrequency ablation was performed and (**c**, **d**) Bone cement injected to strengthen the bone

reduction of the tumour volume which reduced the compression over adjacent nerves and structures. The necrosis causes reduced production of the cytokines as well.

There are many options for the treatment of painful bone metastasis. Treatment options include NASAIDS, opioids, radiotherapy, chemotherapy, radio-pharmaceutical therapy, hormonal therapy, surgery, or cement injection. First line of management is analgesics (NSAIDS and opioids). Radiation therapy has also been tried with some success. Around 70% of patients will experience pain relief after radiation therapy. However, radiation therapy has complications likely due to effect on the adjacent soft tissues and bone necrosis (Botsa et al. 2014; Frassica 2003).

Several preliminary results prove that RF ablation of painful bone metastasis can be very effective in palliative pain control (Thanos et al. 2008; Goetz et al. 2004; Locklin et al. 2004; Callstrom and Charboneau 2007). Poor heat conduction is a limiting factor in the treatment of bone lesions. Microwave ablation has better penetration and conductivity. However, the studies are limited (Simon et al. 2005; Callstrom and Charboneau 2007).

Cryotherapy is another option in management of painful bone metastasis (Rose and Morris 2015). Cryo-ablation is less painful compared to RFA and MWA, and hence general anaesthesia may not be required. Cryo-ablation has also got anaesthetic effect by itself. It can be combined with cementoplasty to augment the strength of the bone along with control of the tumour.

5.7 Other Regions

Thermal ablation of breast tumours, thyroid, and parathyroid lesions are still not fully evolved and their role in palliation in these lesions is not established.

6 Conclusion

Significant improvements in thermal ablation techniques have occurred in the past two decades. Ablation techniques definitely have a role in debulking and relief of symptoms in patients with few cancers under palliative care when other modes of treatment are contraindicated or not effective. The decision for ablation therapy should be taken after a multidisciplinary team meeting.

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Part V

Bleeding Solutions

Bleeding Solutions in the Head and Neck

Prasanna S. Tirukonda

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Abstract

Endovascular transcatheter embolization is a widely recognized first-line treatment in the management of acute and subacute haemorrhages caused by infiltrating tumours of the head and neck. It is also useful in devascularization of the tumours prior to surgical debulking. Endovvascular techniques enable accurate visualization of the pathology and targeted embolization of the culprit vessel. Timely control of haemorrhage may offer patients a reasonable lifespan and improved quality of life.

P. S. Tirukonda (✉)
Department of Diagnostic Radiology,
Changi General Hospital, Singapore, Singapore
e-mail: Prasanna_sivanath_tirukonda@cgh.com.sg

Abbreviations

CBS	Carotid blowout syndrome
CT	Computed tomography
JAF	Juvenile angiofibroma
MRI	Magnetic resonance imaging
NBCA	*N*-Butyl cyanoacrylate (Glue)
PVA	Poly vinyl alcohol

1 Introduction

Head and neck cancers constitute the fifth most common malignant tumours. Laryngeal cancers are the most common, responsible for 48% of all cases (Rzewnicki et al. 2012). A vast majority of patients with laryngeal cancer present at an advanced stage (T3 and T4). Catastrophic

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_17

haemorrhage can result from local recurrence of infiltrative tumours. Acute or subacute haemorrhage is one of the most frightening complications in patients suffering from advanced head and neck cancer. Up to 10% of advanced head and neck tumours are associated with major bleeding secondary to iatrogenic pseudoaneurysm, ulceration, or as sequelae of intra-arterial chemotherapy and local radiation treatment (Chen et al. 2010).

Conventional management options such as application of local pressure, suture closure, nasal packing, surgical ligation, cautery and transfusion of blood products, can prove futile in post-surgical patients due to scarring and altered anatomy. Surgical access can be difficult. Trans-arterial embolization has become an important tool for the control of head and neck bleeding in post-surgical patients or after chemo-radiotherapy. Timely control of haemorrhage may offer patients a reasonable lifespan and improved quality of life (Bachar et al. 2013).

Diagnostic imaging using contrast enhanced CT enables accurate detection of the bleeding vessels and can guide selective endovascular targeting of the culprit vessel (Duggan and Brylsky 1970; Sclafani and Sclafani 1996; Pérez Higueras et al. 2009).

Different types of endovascular treatment approches may be required for vessel injuries caused by radiation or chemotherapy (Chen et al. 2010). Embolization involves deliberate closing of the vessel that supplies the tumour by introducing embolic agents such as particles (e.g. Polyvinyl alcohol, embospheares™), mechanical devices (coils, vascular plugs) or liquids (e.g. N-butyl cyanocrylate (glue), alcohol, Ethylene vinyl alcohol (ONYX)) into its lumen. It is a valuable palliative treatment in controlling haemorrhage, pain and tumour bulk prior to palliative surgical resection. Embolizations can be temporary or permanent depending on clinical requirement.

Embolization treatment is minimally invasive and has an established track record in terms of efficacy and safety in controlling haemorrhage from tumours in various parts of the body. Most treatments can be performed under local anaesthesia and conscious sedation. The post-procedural recovery is quicker, thereby minimizing hospital stay compared to traditional surgical treatments.

1.1 Pre-procedural Consideration

It is important to review available cross-sectional imaging to assess anatomy and to predict any difficulties that could be encountered during the procedure. If required, additional imaging should be performed to assist with the procedure. Increasing availability of hybrid CT scans is immensely helpful in selective targeting of the tumour circulation during the procedure.

Pre-procedure assessment of renal function and clotting profile should be performed with the view to perform prophylactic corrective measures. The patient should be fasted for at least 4 hours, and should remain well hydrated to reduce the risk of contrast induced nephropathy and prevent the potential post-embolotherapy effects of tumour lysis.

2 Management of Acute Haemorrhage

2.1 Epistaxis

Head and neck cancers can cause intractable epistaxis after local tumour irradiation, following surgery, or spontaneous tumour bleeding (Pereira and Phan 2004).

Selective transcatheter embolization of bleeding vessels with embolic agents is an increasingly used treatment for cases of refractory epistaxis, and has been shown to be safe and effective (Scaramuzzi et al. 2001).

2.1.1 Tumour-Induced Epistaxis

Epistaxis can be caused by almost any sino-nasal tumour. The more common tumours include nasopharyngeal carcinoma (NPC) (Fig. 1a–c), haemangioma, hemangiopericytoma, juvenile angiofibroma and metastatic disease. NPC is rare in most parts of the world except in south east

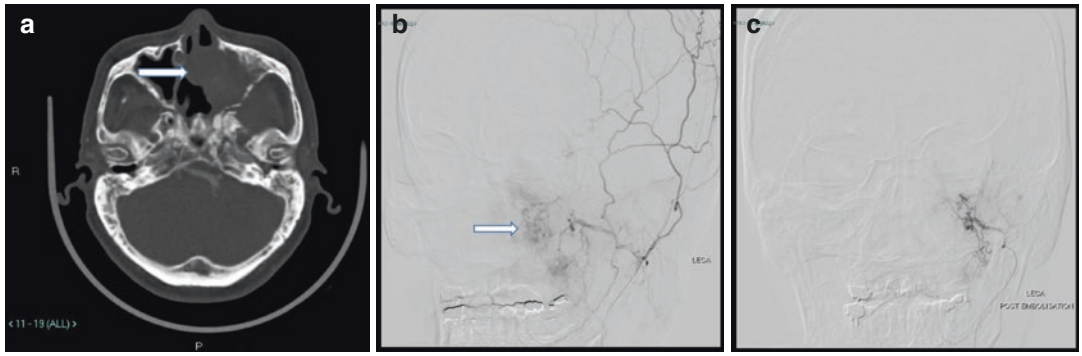

Fig. 1 (**a**) Left Nasopharyngeal Carcinoma (NPC) axial CT scan: Soft tissue mass (arrow) occupying the left nasal; cavity associated with destruction of the left maxillary antrum. (**b**) Left NPC left external carotid angiogram demonstrating tumour blush (arrow). (**c**) Left NPC post-embolization: Note absence of tumour blush

Asia, natives of the arctic region and North Africa.

Juvenile nasopharyngeal angiofibroma (JNA), although a benign tumour accounts for the majority of tumour-related epistaxis. It arises from the posterolateral wall of the nasal cavity, occurring almost exclusively in young males. Embolization of the main feeding arteries can also be performed for preoperative debulking of tumours to reduce significant blood loss during surgery. Angiography is helpful in pre-operative planning, since some angiofibromas are vascularized by both the ICA and ECA with rich collateral arterial supply bilaterally (Wu et al. 2011) (Fig. 2a–d).

2.1.2 Post-treatment Epistaxis

Life threatening epistaxis is a well-known complication following surgical treatments and radiotherapy for sino-nasal tumours. Post-treatment epistaxis can be early due to damage to vessel walls or loosening of ligatures following surgery. Late occurrence can be due to formation of pseudo aneurysms. CT angiography can demonstrate extravasation of contrast medium and can help in identifying the target culprit vessel.

Endovascular treatment is comparable to surgery in terms of adequately stopping the bleeding (overall success rate of 71–100%). Both treatments are similar in terms of complications and treatment failure (Willems et al. 2009).

Embolization of the head and neck requires specific expertise and a thorough knowledge of regional anatomy. Failure to recognize the presence of significant anastomosis between the vascular territories of the nose and the eye or the brain can result in severe complications such as blindness and stroke. On the upside, endovascular treatments are cost-effective, and can be performed under local anaesthesia in most cases.

The choice of treatment should be decided on a case-to case basis, in a multi-disciplinary team setting, taking into account the patients comorbidities, vascular anatomy, availability of equipment and expertise.

2.2 Carotid Blowout

Carotid blowout can be defined as bleeding from the carotid artery or its branches (Fig. 3a–c). It is a dreadful complication of advanced head and neck malignancy and can occur as a complication of surgery or radiotherapy such as radiation-induced necrosis, recurrent tumours, wound complications, or pharyngocutaneous fistulas (Chang et al. 2013; McDonald et al. 2012). Carotid blowout can occur in up to 3–4% of patients following neck dissection (Cohen et al. 2004). Three distinct scenarios can be encountered. A threatened Carotid blowout, when there is imaging or clinical signs that predict future haemorrhage, such as an exposed carotid artery with indistinct wall on imaging or presence of pseudo aneurysm. Imminent carotid blowout is suspected when there is imaging

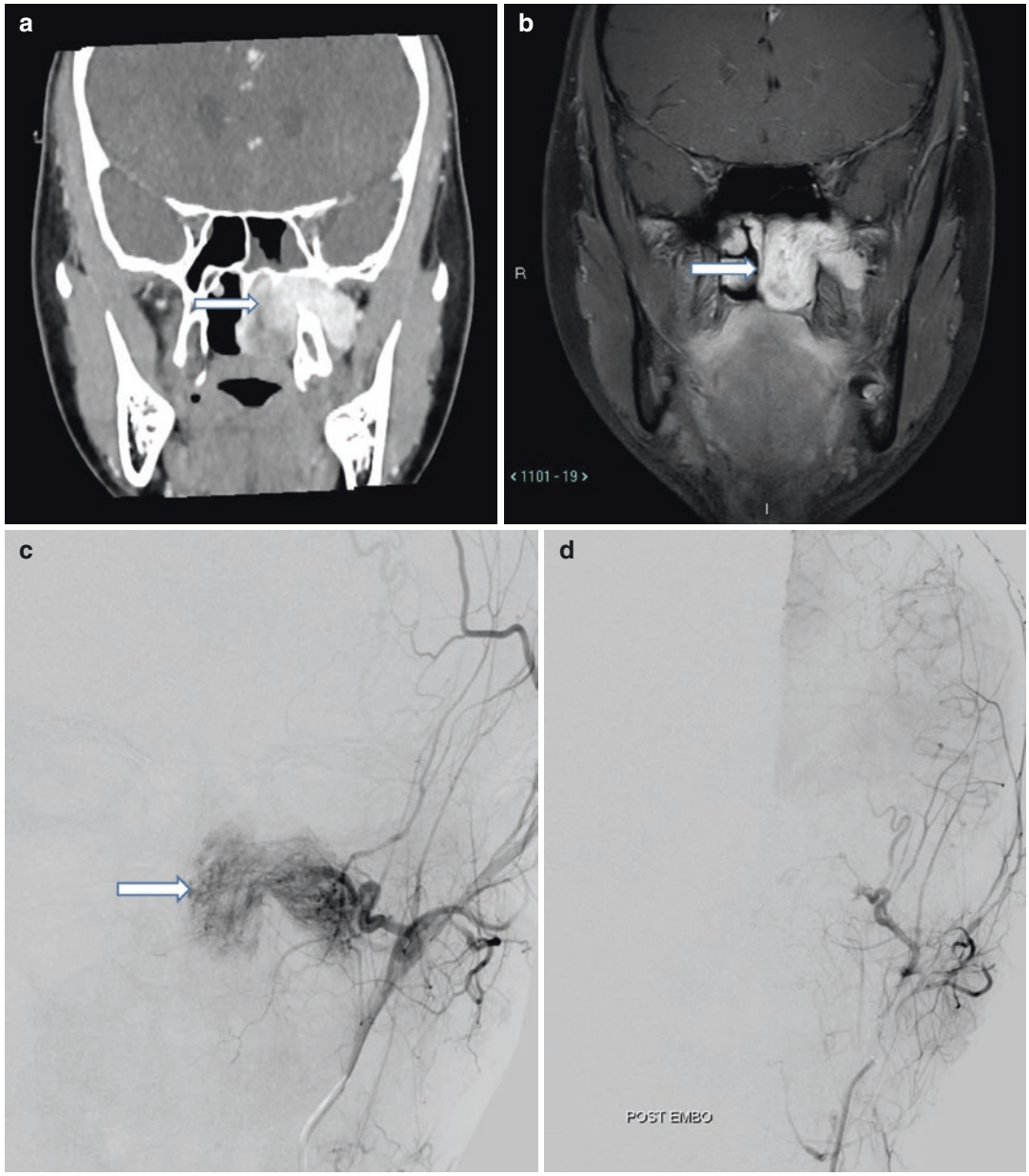

Fig. 2 (**a**) Left juvenile angiofibroma: Coronal CT demonstrates avidly enhancing soft tissue mass arising from the left nasal cavity (arrow). (**b**) Left JNA: MRI T1 fat saturated with contrast. (**c**) Left JNA: Tumour blush on selective angiogram. (**d**) Left JAF, post-embolization. Note absence of tumour blush

evidence of minor bleeding such as haematoma and lastly, acute carotid haemorrhage with active extravasation (Citardi et al. 1995). Surgical treatment for carotid blowout has a mortality of up to 40% and neurological complications of up to 60%. Most of these patients have associated co-morbidity posing high anaesthetic risk. The altered anatomy which results from previous surgery and radiotherapy makes it difficult to identify the source of bleeding (Chaloupka et al. 1996). Due to the dismal outcome, patients with carotid blowout were traditionally managed with end of life comfort measures.

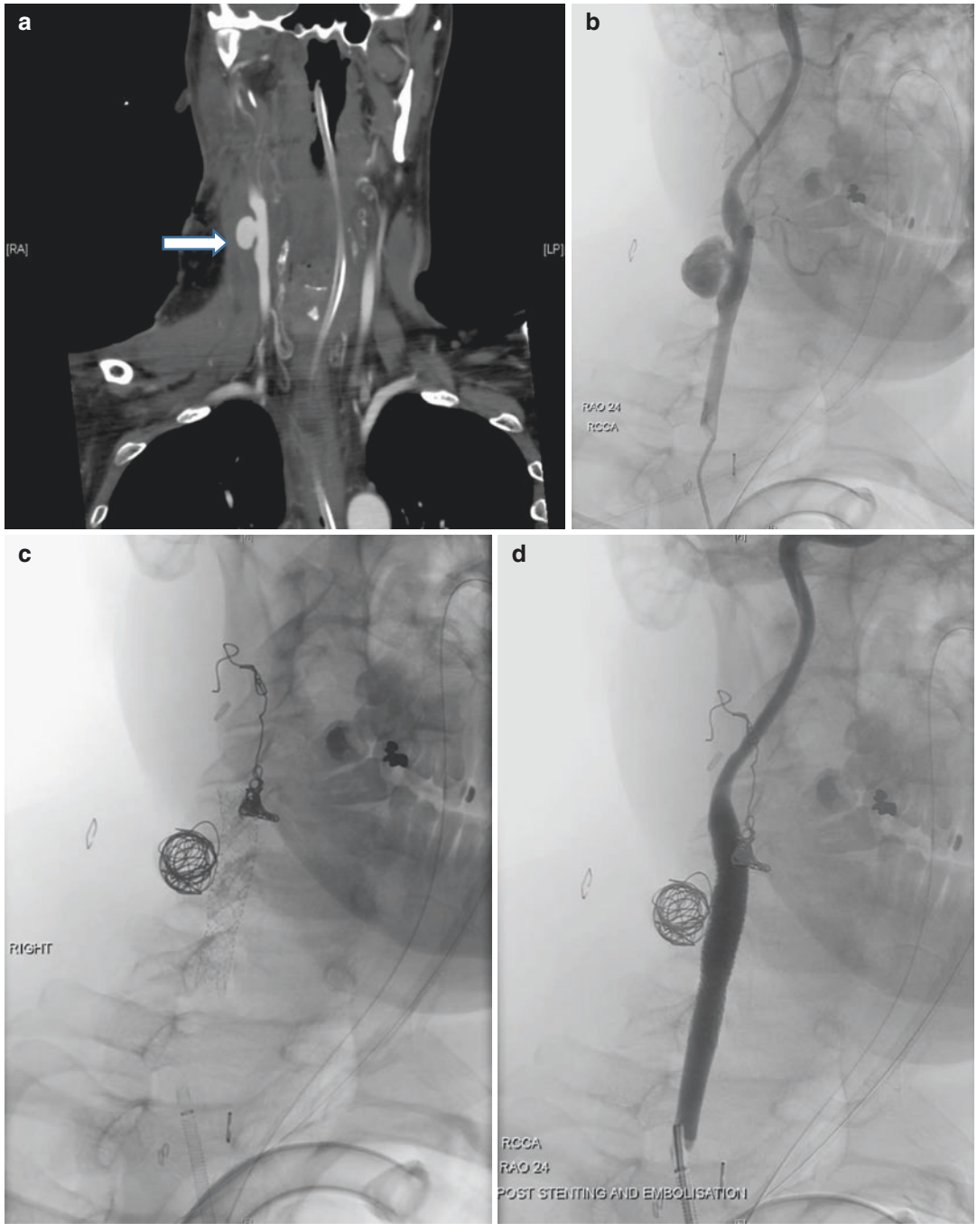

Fig. 3 (**a**, **b**) Right carotid blow out (CBS). CT angiogram (**a**) and conventional angiogram (**b**) demonstrate pseudoaneurysm arising from the right common carotid artery (arrow). (**c**, **d**) Endovascular treatment with coils and stent shows complete exclusion of the pseudoaneurysm. (Image courtesy of Dr. Anil Gopinathan Nair and Dr. Prapul Rajendran, Department of Radiology, National University Hospital, Singapore.)

2.2.1 Role of Endovascular Therapy in Carotid Blowout Syndrome (CBS)

Endovascular treatment is suitable for treating patients with CBS caused by various etiologies. Role of a multi-disciplinary team including the patient (where possible) cannot be stressed enough, in order to decide on the most appropriate treatment that can offer a better quality of life for the patient. There are three endovascular treatment options available.

2.2.2 Permanent Balloon Occlusion (PBO)

A detachable balloon is placed in the common carotid artery, preventing blood flow into the bleeding vessel (Citardi et al. 1995; Lesley et al. 2003). A temporary balloon occlusion test can be performed to predict the risk of cerebral ischaemia. Delayed cerebral ischaemia has been reported in upto 20% of the cases following PBO (Lesley et al. 2003).

2.2.3 Selective Embolization

Targeted image guided embolization of the bleeding vessels can be performed with a variety of embolic agents such as coils, vascular plugs, liquid embolic agents (NBCA, ONYX). The main carotid trunk is preserved (Morrissey et al. 1997).

2.2.4 Endovascular Stent Placement

Reconstructive method with endovascular stent grafts is a promising technique which preserves patency of the carotid vessels and can be performed in combination with embolization (Hakime et al. 2013).

Various studies report varied outcomes for the endovascular treatment of CBS. This is likely due to variations in endovascular practice methods, varied pathology and severity of disease (Chang et al. 2013). Currently there are no standardized treatment algorithms (Zussman et al. 2012). Institutional treatment algorithms can vary depending on availability of endovascular expertise and equipments.

3 Palliative Embolization of Tumours

Preoperative embolization of tumours of the head, neck is used for palliation and is an important adjunct to the surgical debulking in order to minimize operative blood loss. A blood less surgical field offers better visualization for the operating surgeon and may decrease the risk of tumour recurrence (Duffis EJ et al). Highly vascular tumours such as Juvenile nasopharyngeal angiofibroma, Haemangiopericytoma, glomus jugulare and other paragangliomas and metastasis may benefit from preoperative embolization. Pre-procedural CT angiography is useful in delineating the angio architecture of the tumour and its blood supply.

During catheter angiogram, balloon occlusion of the carotid could be performed to identify collateralization with internal carotid branches and predict any possible neurological sequelae (American Society of Interventional and Therapeutic Neuroradiology 2001a; Duffis et al. 2012).

The treatment goal is to achieve devascularization of intra-tumoral vessels by super selective embolization and prevent non-target tissue loss. Preservation of main blood vessels also allows access to the tumour incase of recurrent haemorrhage (Duffis EJ et al).

The procedure is performed by percutaneous trans-arterial access, super-selecting the vessels supplying the tumour. Various embolic agents (temporary or permanent) such as particles, mechanical coils and liquids can be used depending on the blood flow dynamics and operator preference.

Direct puncture of the tumour has also been described in cases of challenging vascular anatomy. This technique is particularly helpful in avoiding non-target embolization, in cases of direct involvement of branches of the internal carotid artery. Ideally the procedure should be performed 72 h prior to surgery. This allows for formation of stable thrombus within the embolized vessels (Gemmete et al. 2009). Recent studies have shown significant reduction in intra-operative blood loss in patients subjected to pre-operative embolization compared to surgery alone (Ahmad S).

4 Limitations of Endovascular Treatment

The site and extent of the tumour, inaccessibility, potential for end organ injury and non-target embolization especially in the vicinity of vessels supplying the central nervous system are potential limiting factors. These can vary with individual patients. A multidisciplinary discussion and individualised approach is therefore imperative to optimize patient care and treatment benefits. The potential risks and benefits of the procedure should be discussed with the patient.

5 Post-procedural Consideration

There are potential risks and side-effects of embolization. Puncture site-related complications include bruising/haematoma, bleeding, or vessel occlusion. Any embolization procedure may be associated with the post-embolization syndrome. This includes varying degrees of pain at the site of embolization, nausea/vomiting, and flu-like symptoms. These are related to tissue ischaemia/necrosis and may last for several days following embolization. The patient should be optimized for peri-procedural and post-procedural analgesia. Anaesthesia/pain management expertise should be involved where possible. There is the potential for critical ischaemia/infarction of organs at or adjacent to the site of treatment as a result of non-target embolization. Target treatment site-specific complications in the vicinity of central nervous system may include stroke, intra cranial bleeding and cranial nerve palsy. Contrast induced nephropathy can be minimized by optimizing peri procedural hydration.

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Gastro-intestinal Bleed

Sivasubramanian Srinivasan

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Abstract

Gastro-intestinal bleed is not uncommon in patients under palliative care. The bleeding can be due to gastro-intestinal malignancies, coagulopathy or bleeding diathesis, or non-neoplastic conditions such as inflammation, peptic ulcer disease, vascular abnormalities, or infection. Such bleeding can be from arterial source. Portal venous source includes bleeding varices. Interventional radiology (IR) has a significant role in controlling bleed in these group of patients (Ramaswamy et al., World J Radiol 6:82–92, 2014). Once the source of bleed is identified, the arterial source can be embolized by selective/superselective transcatheter embolization. TIPSS or BRTO are performed in select cases of variceal haemorrhage.

S. Srinivasan (✉)
Department of Diagnostic Radiology, Khoo Teck Puat Hospital, Yishun Central, Singapore, Singapore
e-mail: srinivasan.sivasubramanian@ktph.com.sg

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_18

1 Introduction

Gastro-intestinal (GI) bleed in palliative care patients can be broadly classified into patients with malignancies and patients under palliative care for non-malignant diseases such as terminal lung disease, advanced liver disease, end-stage renal failure, advanced dementia or intractable neurological disorders and cardiac conditions (Niekamp et al. 2017; Mørch and Davidson 2007) (Fig. 1). The goal of management in patient under palliative care with GI bleed includes reduction in transfusion requirements, stoppage of bleed and bridge to surgery in select patients (Hirahara 2004).

2 Clinical Assessment, Resuscitation, and Initial Management (Ramaswamy et al. 2008)

Clinical history and all past records should be reviewed. Clinical examination and monitoring of vital signs should be performed at presentation. In cases of haemodynamic instability, fluid resuscitation and if needed transfusion of blood products is necessary. Ionotropes may be necessary to improve the blood pressure. If the blood tests suggest coagulopathy, it should be corrected. It is very important to determine the source of bleeding whether it is from the upper GI or lower GI tract. Upper GI bleed (proximal to ligament of Treitz) presents as haematemesis or malaena; and lower GI bleeding presents with fresh per-rectal bleeding. In cases of upper GI bleeding, endoscopy is the initial investigation of choice, not only for diagnosis but also for treatment such as banding of varices, injection of epinephrine and placement of metallic clip. Factors which predict failure of endoscopy include shock, significant comorbidities, Hb < 10 g/dL and >10 units of blood transfusion. Placement of metal clip may also serve as a marker for the site of bleed during angiography.

For lower GI bleed, if it is an active bleed, colonoscopy may not be very helpful (Romaric Loffroy 2012).

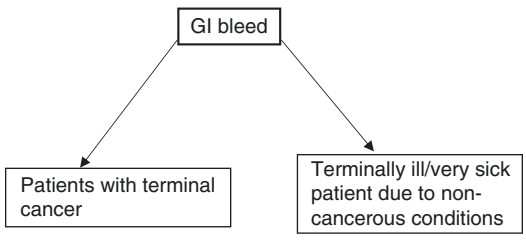

Fig. 1 Flow diagram showing the categories of patients under palliative care presenting with gastro-intestinal (GI) bleed

3 Role Computed Tomographic Angiography (CTA) (Ramaswamy et al. 2014; Wortman et al. 2017)

CTA can detect active bleeding when the rate of bleeding is 0.3 mL/min. At our institution, we perform a non-contrast scan followed by arterial and venous phases by injecting contrast at the rate of 4–5 mL/s. Oral contrast is not administered for patients with GI bleed. Non-contrast computed tomography (CT) may be helpful in showing the dense clot within the lumen (especially the sentinel clot). Post-contrast phases show exactly the site of bleeding with pooling of contrast within the lumen in venous and delayed phases. In cases of upper GI bleed, CTA is useful when endoscopic techniques fail to control the bleed or when endoscopy is not possible. The CT angiography also serves as a road map for angiography. In patients with active lower GI bleed, CT is the modality of choice for diagnosing the source and cause of the bleed.

4 Role of Scintigraphy (Ramaswamy et al. 2014)

Rarely nuclear scintigraphy has a role in identifying the cause of lower GI bleeding when CTA is negative, especially when rate of bleeding is around 0.1–0.3 mL/min. Technetium—99m labelled RBCs are injected and monitoring can be performed up to 24. This is useful when the bleeding is intermittent.

5 Embolization Agents (Vaidya et al. 2008; Kondo 2009)

The various embolic materials are summarized in the flow diagram (Fig. 2).

The choice of the embolic agent depends on whether the desired occlusion is temporary or permanent. The level of embolization can be proximal or distal. In patients with cancer there will be continuous angiogenic stimulus and hence proximal occlusion with result in failure. In oncological and chronic inflammatory process, distal embolization is often performed and the best embolic agent is particles such as polyvinyl alcohol (PVA) and less often liquid agents. However the disadvantages of distal embolization are risk of ischaemia and tissue necrosis. The choice of embolic agents and common risks are summarized in the table (Table 1).

5.1 Particles

Gelfoam (Gelfoam, Kalamazoo) is a porcine derivation and is used as surgical haemostatic. It is used as embolic material for bleeding control. Usually the commercially available gelatin sponge sheet is cut into smaller size (1–6 mm) and then loaded into syringes and mixed thoroughly with appropriately diluted contrast using three-way taps and two Luer-Lock syringes. During mixing or agitation, the particles may be broken into smaller sizes. The particles Gelfoam effectively produces arterial and capillary occlusion. However there is a risk of ischaemia if the particles are too small and in vulnerable areas of gastro-intestinal tract such as the splenic flexure of the colon. Gelfoam can be used alone or in combination with coil or plug to obtain complete haemostasis especially when the patient has abnormal coagulation profile.

5.1.1 Polyvinyl Alcohol (PVA) Foam

It is the product of polyvinyl alcohol and formaldehyde. It is an inert material and is considered safe. These may be non-spherical particles or PVA microspheres (which are relatively new). Non-spherical PVA particles occlude the vessels by mechanical occlusion along with thrombus formation between the particles. PVA is available in various sizes such as 100–300 to 900–1200 microns.

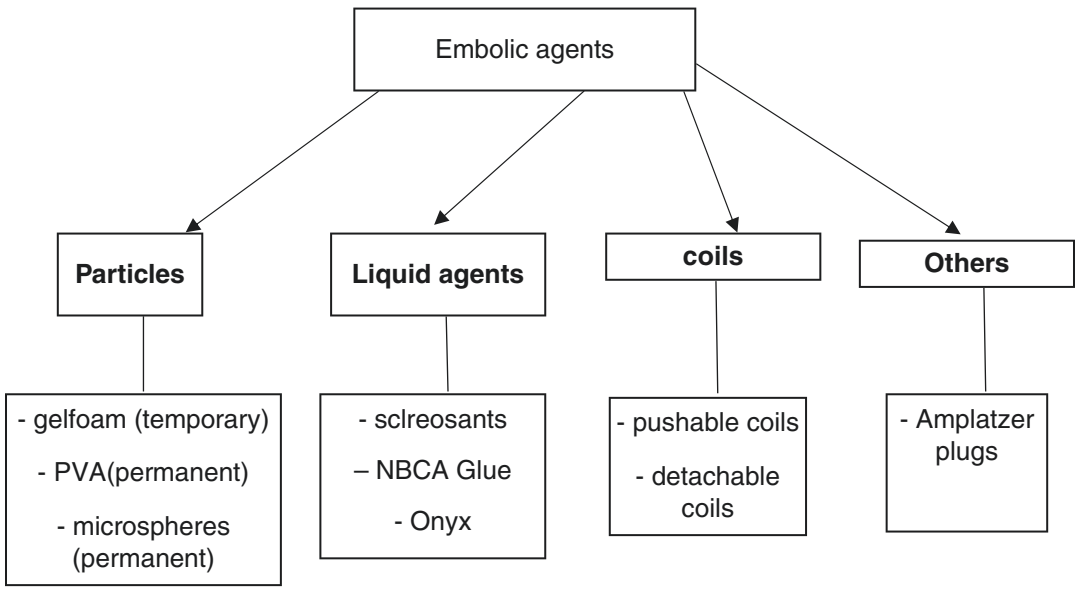

Fig. 2 Flow diagram showing the various types of endovascular embolic agents used to treat acute bleed

Table 1 Common causes of GI bleed and most suitable embolic agent

Conditions	Choice off embolization material	Risks
BRTO/Variceal embolization	1. Glue 2. STS	Glue—difficult to control; non-target embolization
Upper GI bleed (non-neoplastic cause)	Glue, coils	Non-target embolization
Tumour (upper or lower GI)	Particles (Gelforam/PVA/newer particles), glue	Ischaemia, non-target embolization
Lower GI bleed (non-neoplastic cause)	Coils rarely particles/glue	Ischaemia, non-target embolization

5.1.2 Other Particle Agents

Calibrated microspheres consisting acrylic beads with gelatin (tris-acryl microspheres) (Embosphere, Biosphere Medical, Roissy, France). These spherical particles are available in preformed syringes and are able to pass through microcatheters without clumping or getting deformed.

Microspheres made of polymethylmethacrylate with thin coating (Embozene, Celonova, Newnan, GA, USA) are another type of particles which are colour coded in syringes. These are also available in various sizes.

5.2 Liquid Agents

These include glue such as N-butyl cyanoacrylate (NBCA), elastic polymers such as ethylene vinyl alcohol/dimethyl sulfoxide (Onyx), sclerosant agents such as absolute alcohol and sodium tetradecyl sulphate (STS) and lipiodol (iodized oil).

5.2.1 Glue/NBCA

Highly adhesive material which can polymerize when it comes in contact with any ionic surfaces. When using NBCA, polycarbonate syringes should be avoided (due to risk of damage) and polyethylene or polypropylene syringes should be used. NBCA is usually mixed with lipiodol for opacification, and this mixture extends the polymerization time as well. The mixture can be 1:2–1:5. The catheter system is flushed with 5% dextrose and use of saline is avoided when the glue is used. Usually, the microcatheter used after injection of the glue is discarded and rarely reused after flushing well with dextrose 5%. NBCA is useful especially in upper gastro-intestinal bleeding (for gastric or gastro-duodenal artery branches). However, use of glue needs good expertise and experience to avoid non-target embolization. The stability of catheter and microcatheter is very important.

5.2.2 Ethylene Vinyl Alcohol/ Dimethyl Sulfoxide (Onyx)

Onyx is a non-adhesive polymer. It comprises of ethylene vinyl alcohol (EVOH) dissolved in dimethyl sulfoxide (DMSO) and suspended tantalum powder. It comes in two forms—Onyx 18 containing 6% of EVOH and Onyx 34 containing 8% EVOH. The viscosity of Onyx 18 is less and can cause more distal embolization compared to Onyx 34. Once injected, the polymer forms a slow solid cast within the vessel. Onyx does not adhere to the tissue unlike NBCA glue. DMSO compatible syringes and microcatheters should be used. The mixing of Onyx takes around 20 min and mixing should be done till it is ready to be injected. Initial flushing is done with normal saline and then the microcatheter is flushed with DMSO. With syringe held vertically upwards Onyx is injected very slowly (around 0.16–0.2 mL/min). Care should be taken that reflux is avoided. On completion, the catheter is removed after few seconds. Onyx is mainly used in cerebral arterio-venous malformations, but recently it has been used in peripheral visceral embolizations.

5.2.3 Sclerosants

Among the sclerosants, sodium tetradecyl sulphate (STS) is the one used in treatment of variceal bleed. It is an anionic surfactant/detergent which can cause inflammation and thrombus formation. The STS is commercially available as 0.2% and 3 (2 mg/mL and 30 mg/mL,

respectively). Foam is created by mixing STS with air (usually 1:4) and injected into the vessel (portal varices). It should not be used in patients with hypersensitivity and in arterial source of gastro-intestinal bleeding.

5.3 Coils, Plugs, and Occlusion Devices

Ideal vascular occlusion device should be simple to deploy, easy to deliver with simple catheter system, able to allow precise deployment and resistant to migration from deployed position, should be inert and not cause any inflammation and absent or very low rate of chronic complications. These devices include coils and vascular plugs (such as Amplatzer plug).

5.3.1 Coils

Coils are spiral metallic filaments which are delivered through a catheter or microcatheter into the target vessel to be embolized. Most of them have fibres braided over them which help to accelerate thrombosis. The coils are made of steel, platinum, or alloy. Stainless steel coil are more radio-opaque but are prone for artefacts in magnetic resonance (MR) imaging. Platinum coils are very flexible. Coils can be pushable or detachable (based on the mechanism of deployment). Detachable coils have more control and are being increasingly used recently.

6 Causes of GI Bleed

The causes of GI bleed are summarized in the flow diagram (Fig. 3).

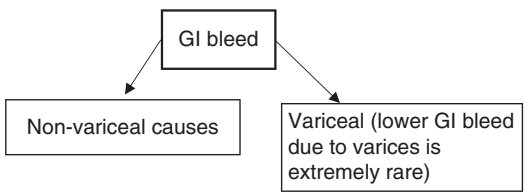

Fig. 3 Flow diagram showing the causes of upper and lower GI bleed in adult patients under palliative care

6.1 Non-variceal GI Bleed

6.1.1 Upper GI Bleed

(Lee and Laberge 2004)

1. General causes such as bleeding diathesis, coagulopathies.
2. Tumours—primary or secondary.
3. Peptic ulcer disease.
4. Vascular malformations.
5. Other causes—Aortoduodenal fistula Haemobilia.

6.1.2 Lower GI Bleed

(Lee and Laberge 2004)**:**

1. General causes such as bleeding diathesis, coagulopathies.
2. Tumours—primary or secondary.
3. Inflammation (diverticulitis/colitis).
4. Angiodysplasia/vascular malformations.
5. Others: Haemorrhoids, rectal ulcer, anal fissure, Aortocolonic fistula, anastomotic bleeding, faecal impaction.

6.1.3 Angiography and Embolization (Non-variceal Bleed)

For non-variceal source of bleeding, right femoral arterial access is the choice. Radial access may be used to minimize bleeding in cases of thrombocytopenia or coagulopathy. Choice of catheters include forward curve catheters such as Cobra catheters or reverse curve catheters (especially for inferior mesenteric artery). Use of iodinated contrast should be minimized in patients with renal failure. Angiography of the target artery (Celiac artery/superior mesenteric artery (SMA) or inferior mesenteric artery (IMA)) should be performed and the site of bleeding should be confirmed. Superselective catheterization should be performed with a microcatheter and embolization of the targeted vessel (s) should be performed (Figs. 4 and 5). Important complications of embolization includes non-target embolization, dissection of vessels, pseudoaneurysm, failure of embolization, and ischaemia of the bowel (Shin 2012; Werner et al. 2018; Romera Barba et al. 2014; Navuluri et al. 2012).

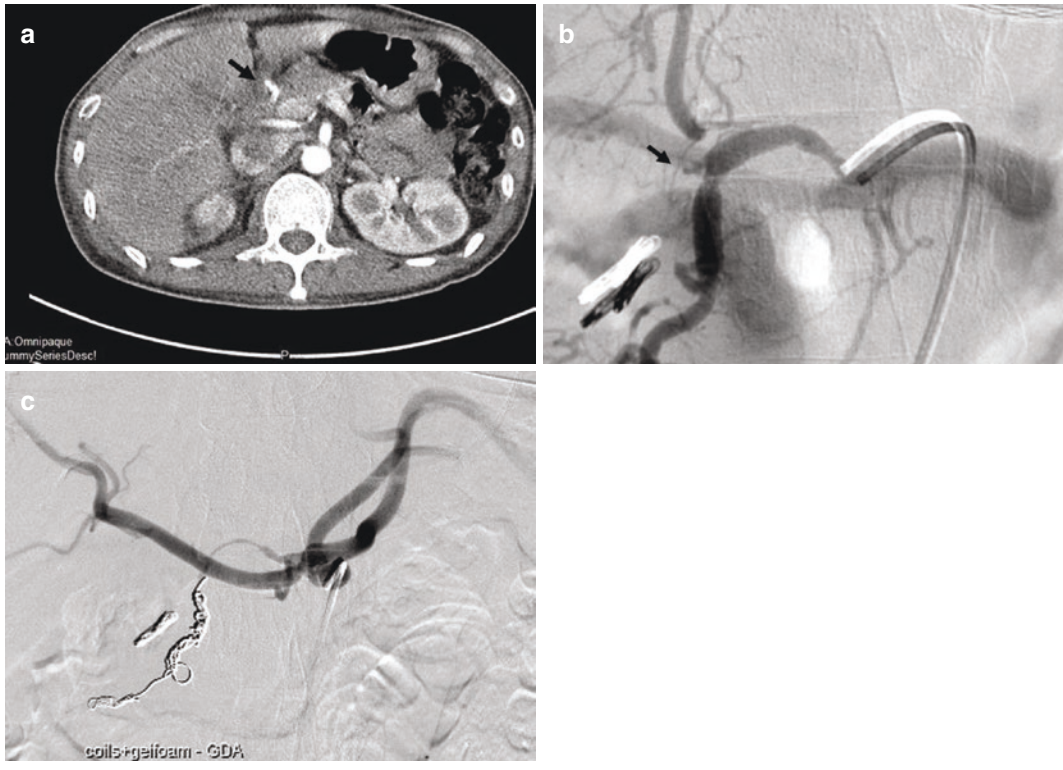

Fig. 4 Upper GI bleed due to a pseudoaneurysm of GDA in a patient with multiple comorbidities. Endoscopic management was not successful. (**a**, **b**) CT Angiogram and catheter angiogram showing proximal GDA pseudoaneurysm (arrow). (**c**) Post-embolization angiogram. Embolization was done with gelfoam particles and coils

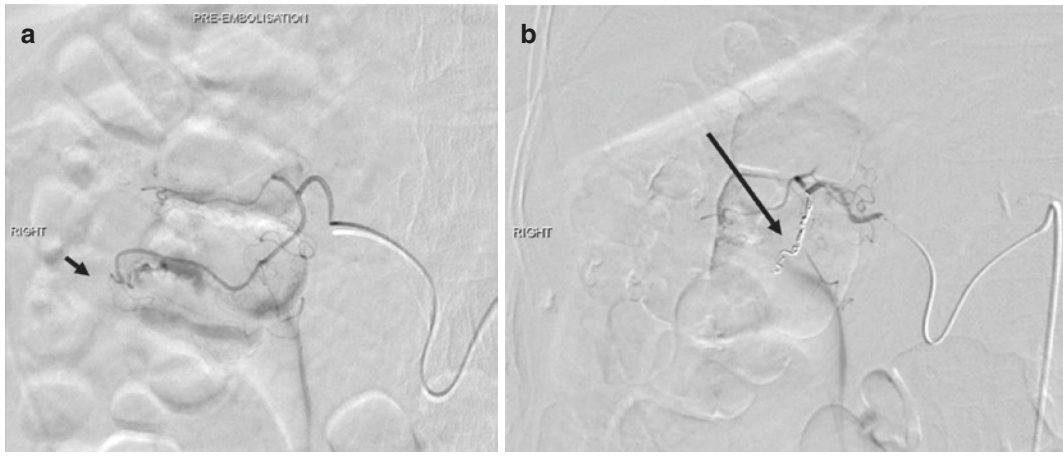

Fig. 5 Lower GI bleed due to diverticular haemorrhage. (**a**) Selective angiogram of right colic artery branch showing active extravasation. (**b**) Angiogram after embolization of the artery with coils

6.2 Variceal Bleed

It is important to identify the source of upper GI bleed and differentiate variceal bleed from non-variceal bleed (which is usually from an arterial source). Gastric varices are known to around one-third of deaths in patients with cirrhosis is due to variceal bleed. Variceal bleed is a sequelae of portal hypertension. However, around one-third of patients with portal hypertension have arterial source of bleeding (Navuluri et al. 2012; Lee and Laberge 2004).

Endoscopic haemostasis is the first line of treatment in patients with variceal bleed after initial stabilization. Endoscopic management of oesophageal varices includes ligation of the varices or injection sclerotherapy. The gastric varices can be classified into isolated gastric varices and gastro-oesophageal varices if the oesophageal varices cross beyond the gastro-oesophgeal junction. The gastric varices which are especially located in the body/antral region are usually treated by injection sclerotherapy. If the endoscopy techniques fail, treatment options include balloon tamponade with Sengstaken–Blakemore tube and usually the success rate is around 80% for lower oesophageal or gastro-oesophageal varices. However, this method should not be used more than 24 h.

Transhepatic intrahepatic porto-systemic shunt (TIPSS) and balloon occluded retrograde transvariceal obliteration (BRTO) are methods evolved to treat complications of portal hypertension especially in patients with variceal haemorrhage (Lipnik et al. 2018).

6.2.1 TIPSS

The transjugular intrahepatic porto-systemic shunt (TIPSS) is indicated in variceal haemorrhages which are refractory to endoscopic management. Other indication is refractory ascites in patients with decompensated liver (Navuluri et al. 2012). Relative contraindications include heart failure, acute liver failure, hepatic encephalopathy, untreated biliary obstruction, liver tumours, and uncontrolled coagulopathy.

Preprocedure workup includes risk stratification based on Model for End-Stage Liver Disease (MELD) score which helps in assessing prognosis. Patient's comorbidities and relevant lab tests should be checked. Cross-sectional imaging should be carefully studied for the anatomy of the vessels, presence or absence of important porto-systemic collaterals, liver lesions, ruling out biliary obstruction, and planning of approach.

The right hepatic vein is catheterized and a hepatic venography is performed. Wedge pressures may be measured and wedge hepatic venogram is performed which helps to opacify the right portal vein. A needle is then directed into branch of right portal vein and sheath is advanced into the portal vein. Portal pressures are then measured and after dilatation of the tract, a suitable sized stent graft such as Viator (W.L Gore, Glagstaff, AZ) is deployed. The dilatation of tract is aimed to reduce the porto-systemic gradient to 12 mmHg or less (Fig. 6). After creation of the TIPSS, variceal embolization can be considered.

After the procedure, patient should be carefully monitored for resolution of varices and potential complication of TIPSS which includes bleeding, hepatic encephalopathy, cardiac failure, or worsening of renal function. Shunt patency should be checked at 1, 3, and 6 months by Duplex Doppler.

6.2.2 BRTO

Balloon occluded retrograde transvariceal obliteration (BRTO) is popular mainly in Asia. It is mainly performed to treat gastric varices. This is typically performed in patients who are high risk for TIPSS, such as right heart failure, high MELD score or hepatic encephalopathy (Navuluri et al. 2012).

Contraindications include thrombosis of portal or splenic vein without other porto-systemic collateral pathway. Preprocedure evaluation includes endoscopy to assess the presence of gastric varices and to rule out oesophageal varices. Cross-sectional imaging helps in planning for the procedure and to assess the various collateral presence. It also helps to identify other complications of portal hypertension such as ascites or splenomegaly.

The shunt is usually performed through gastro-renal shunt. However, experienced operators may be able to perform BRTO through other shunts such as inferior phrenic vein or less common shunts (Fig. 7).

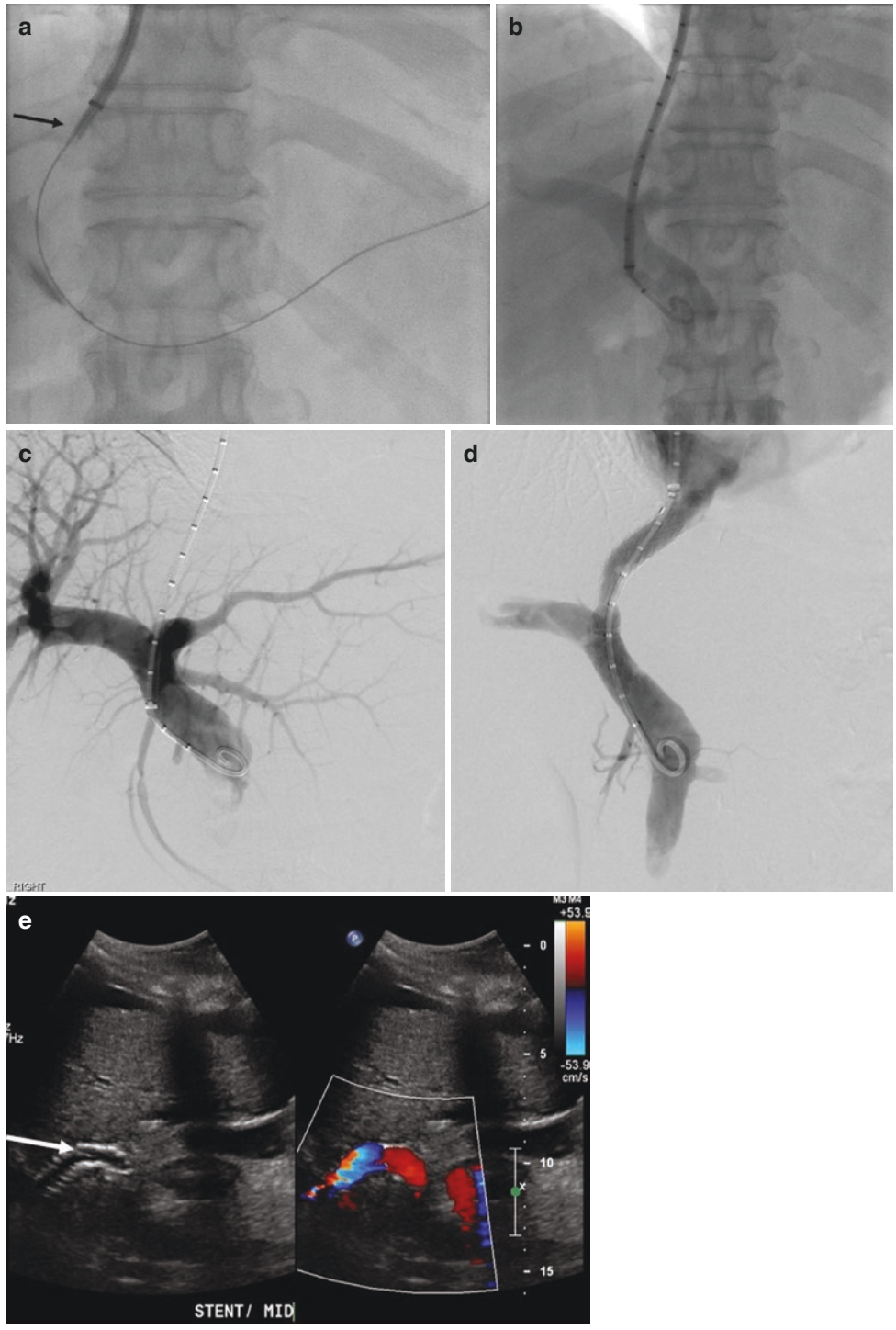

Fig. 6 TIPSS for refractory ascites due to chronic liver disease. (**a**) Access from right hepatic vein (sheath shown with arrow) to portal vein. (**b**, **c**) Pigtail porto-venogram through the hepatico-portal tract. The markings in the pigtail helps to measure the size of the stent needed (**d**) Post-deployment of the stent graft and balloon dilatation. Smooth flow was observed. (**e**) Surveillance ultrasonography (US) scan after 1 year showing patency of the TIPSS

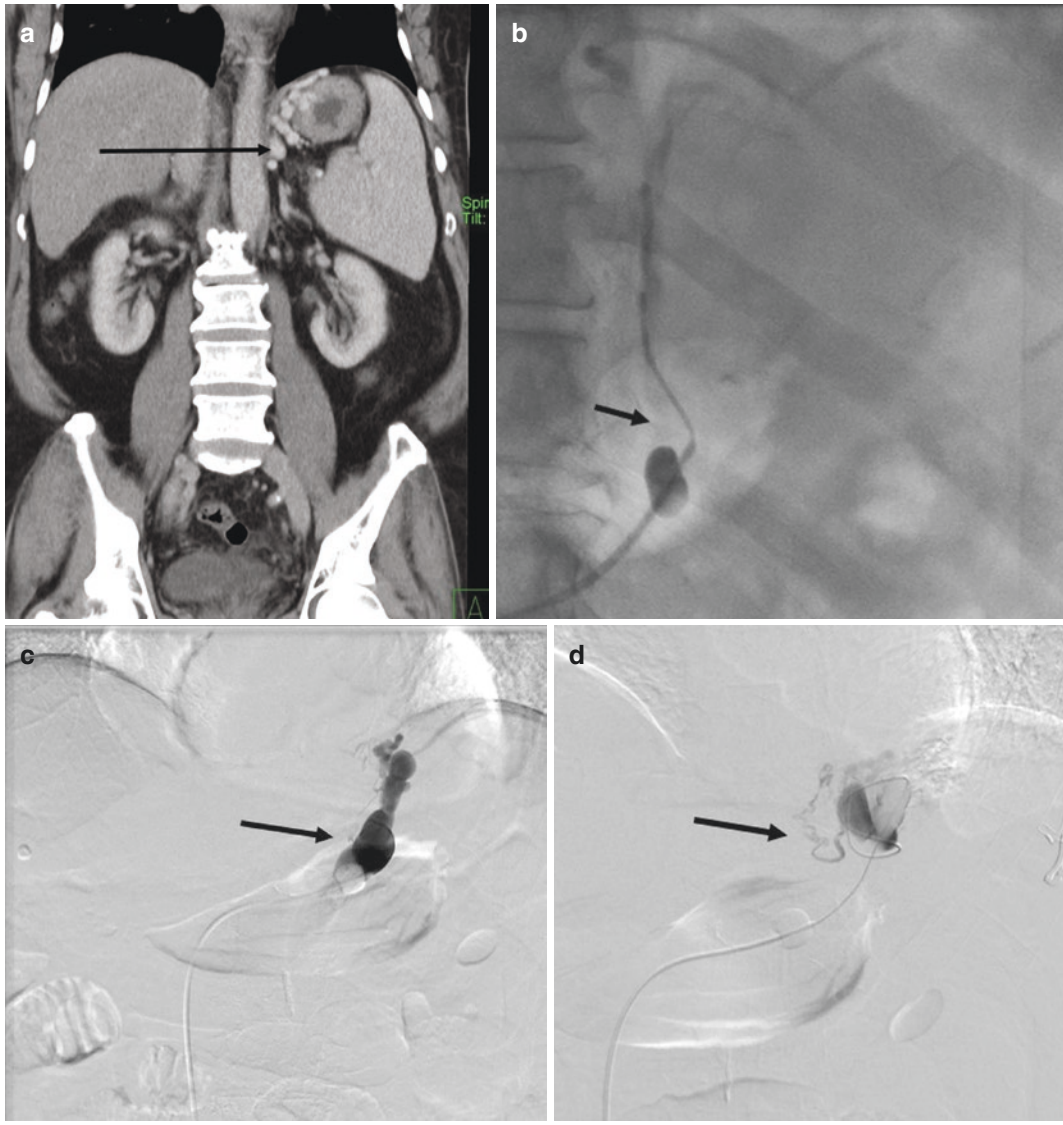

Fig. 7 BRTO for gastric varices. (**a**) Contrast-enhanced CT (coronal section) showing large gastric varices (**b–d**) Balloon catheter in the splenorenal shunt with contrast opacification of the varices. (**e**) Post-embolization of the gastric varices (dense lipiodol within the occluded varices)

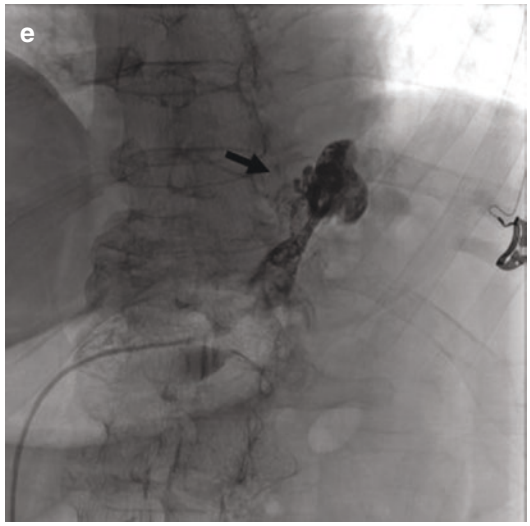

Fig. 7 (continued)

7 Conclusion

Gastro-intestinal bleeding can be a cause of bleeding in patients under palliative care. It may be refractory to medical therapy and endoscopic management. In such cases, imaging and endovascular intervention can help in cessation of bleeding and improving the haemodynamic stability of the patient.

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Bleeding Solutions for Genitourinary Tract

Apoorva Gogna and Farah Gillan Irani

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Abstract

Bleeding from the genitourinary tract can significantly reduce quality of life, escalate costs in the palliative care setting and cause death. Gross painful haematuria can cause extreme distress to patients and care providers and require emergency medical intervention (Groninger and Phillips 2012). On the other side of the spectrum, painless microscopic haematuria may result in chronic anaemia, need for frequent blood transfusions, repeated medical interventions and increased cost of care for patients. In this chapter, we discuss the palliative interventional management of this important entity.

A. Gogna · F. G. Irani (✉)
Department of Vascular and Interventional Radiology, Singapore General Hospital, Singapore, Singapore
e-mail: farah.gillan.irani@singhealth.com.sg

1 Introduction

The spectrum of genitourinary tract disease in terminally ill patients includes infections, urinary tract obstruction, fistula formation, pain and intractable bleeding (Lee et al. 2015). Bleeding may manifest externally as haematuria (most common), per vaginal bleeding, haematospermia or internal haemorrhage. As patients in this category are often debilitated, non-surgical management is frequently required for control of

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_19

intractable bleeding (Hulme and Wilcox 2008). In this chapter, we will discuss the relevant presentations and disease entities, adjunctive management and interventional radiological solutions for genitourinary bleeding in the palliative care setting.

2 Disease Presentations and Adjunctive Therapy

2.1 Haematuria

Haematuria is most commonly from bladder or renal origin and may be broadly categorized as painless or painful; microscopic or gross. Relevant aetiologies for this chapter include tumour sloughing, radiation cystitis, fistulation into vessels and drug-induced (e.g. cyclophosphamide) haemorrhagic cystitis (Lee et al. 2015; Pereira et al. 2016; Ghahestani and Shakhssalim 2009). Other causes such as calculi, trauma, infection and glomerular disease should be excluded (Groninger and Phillips 2012). Exacerbating factors include anticoagulant medications, impairment in synthetic function and poor wound-healing (Lee et al. 2015); a recent retrospective study found that occult genitourinary carcinoma, particularly bladder cancer may be unmasked by anticoagulation therapy (Yu et al. 2017).

Forty percent of patients with renal cancers may present with haematuria (Neeman et al. 2005). Refractory gross haematuria may present with painful acute obstruction due to clot retention, secondary infection and be potentially life-threatening. Initial treatment includes urinary catheterization, bladder irrigation and blood transfusion. Workup include urine culture and cytology, upper urinary tract imaging with multiphase CT and urinary bladder evaluation with cystoscopy (Pereira et al. 2016). Systemic contributing factors for bleeding such as drug therapy (Yu et al. 2017; Kodani 2017) (e.g. anti-platelet agents, prophylactic anticoagulation) and abnormalities in clotting factors or platelet levels should be excluded.

2.1.1 Advanced Bladder Cancer

Intractable haematuria in patients with advanced bladder cancer may be related to direct tumoural haemorrhage or post-treatment effects (e.g. related to cyclophosphamide-induced haemorrhagic cystitis or radiation cystitis) (Ghahestani and Shakhssalim 2009).

Adjunctive options include systemic and topical therapy, radiotherapy, endoscopic procedures and surgical procedures (Schuhrke and Barr 1976). Anti-fibrinolytic agents (e.g. tranexamic acid and aminocaproic acid) may help to stabilize the formed blood clot. Specialized topical procoagulants, e.g. thromboplastin powder, fibrin sealants and gelatin powder are effective but often insufficient in isolation. Topical cauterizing or vasoconstricting agents, e.g. prostaglandin E2, formalin, silver nitrate, aluminium astringents and sucralfate have yielded variable levels of success ranging from 54 to 90%, at the expense of severe complications such as incontinence, reduced bladder capacity, ureteral fibrosis, retroperitoneal fibrosis, aluminium encephalopathy and severe lower urinary tract symptoms (Ghahestani and Shakhssalim 2009). Vasoactive drugs, e.g. octreotide and vasopressin may have a role when bleeding is related to splanchnic blood flow (e.g. lesions invading the gastrointestinal tract).

Palliative external beam radiotherapy has reported efficacy rates of 60% for haematuria from bladder cancer. However, patients who have received prior radiotherapy to the same field may be potentially excluded from further radiotherapy sessions (Ghahestani and Shakhssalim 2009). Intravesical hyperbaric oxygen therapy yielded an 85% success rate for haemorrhagic cystitis, at the cost of multiple treatment sessions (at least 20 sessions), albeit with no obvious adverse effects (Ghahestani and Shakhssalim 2009).

The surgical option of urinary diversion excludes the urinary bladder from the effects of urokinase in the urine, creates a closed system for internal tamponade and allows for instillation of agents such as formalin with less of the attendant side effects. Alternatively, palliative cystectomy may be offered when anatomically suitable, possibly with neoadjuvant chemotherapy.

Embolotherapy has been reported in various retrospective studies with response rates up to 90% however, as with all modalities, comparative data is limited. Two forms of embolotherapy can be considered in this context. Firstly, arterial occlusion (usually hypogastric artery embolization) is employed in cases of sloughing tumour and less commonly radiation cystitis. Secondly, urinary diversion is employed with a combination of percutaneous nephrostomy (PCN) and ureteric embolization. The combination of arterial and urinary occlusion, termed "bladder urovascular segregation" may be useful to avoid the morbidity of cystectomy (Ghahestani and Shakhssalim 2009). Further, PCN treats the partial or complete renal obstruction that affects many patients with advanced bladder cancer.

2.1.2 Prostatic Bleeding

The two most common sources of intractable haematuria of prostate origin are benign prostatic hyperplasia (BPH) and prostate cancer (Pereira et al. 2016). Conservative management approaches include supportive therapy (intravenous fluids, blood transfusions, bed-rest), urinary bladder catheterization and bladder irrigation (Hicks and Li 2008). Supplemental 5-α-reductase inhibitor therapy (finasteride) and androgen agonists have been reported to have some efficacy in BPH (Pereira et al. 2016; Rastinehad et al. 2008a); however, they are slow acting and probably have limited role in the palliative population. Intravesical administration of cauterizing agents such as aluminium sulphate, silver nitrate, ε-aminocaproic acid and formaldehyde may have a limited adjunct role in conservative management of prostatic bleeding (Pereira et al. 2016; Singh and Laungani 1992).

Surgical management which includes transurethral resection of prostate (TURP), prostatic photo-vaporization, trans-urethral or trans-rectal balloon tamponade is often suboptimal in this group (Pereira et al. 2016; Mohyelden et al. 2015). Super-selective minimally invasive endovascular techniques may hence save the patient considerable disease-related and treatment-related morbidity.

2.2 Vaginal Bleeding

Vaginal bleeding incorporates a broad range from normal cyclical menstrual bleeding to pregnancy-related haemorrhage to intractable vaginal bleeding resulting from malignancy. Sources of haemorrhage include the vaginal wall, cervix, uterus and rarely fallopian tubes. During workup and differential diagnosis of significant non-menstrual vaginal bleeding, arterial phase imaging (CT or MR) of the pelvis should be incorporated to provide anatomic details relevant for subsequent endovascular therapy. As tumour-related genital tract bleeding is often slow, active extravasation may not be demonstrated on angiographic imaging; however, selective embolotherapy of the tumour can still proceed based on the arterial supply.

Adjunctive management options include high-dose progesterone for endometrial cancer, surgical packing of vaginal canal, pelvic radiotherapy and surgical exenteration. These methods are effective but have significant limitations (Field et al. 2016). Vaginal packing needs to be changed every 2–3 days and can traumatize friable tumour tissue, resulting in episodic rebleeding with every change of pack. Further, the procedure is painful, and frequently requires general anesthesia. Hypofractionated radiotherapy for control of bleeding may require multiple fractions to achieve haemostasis and compromise later curative radiotherapy (Field et al. 2016). Surgery may be difficult or impossible. For example, advanced cervical cancer with pelvic side wall invasion often excludes hysterectomy as a viable option. Surgical internal iliac artery ligation (described in past literature) is technically difficult, often insufficient due to extensive pelvic collateral network and hence has mostly been superseded by selective transcatheter embolization.

3 Interventional Radiology Procedures

Interventional radiology techniques are important in this predominantly frail and elderly patient population because they can usually be

performed under local anaesthesia. These treatments are minimally invasive, effective and repeatable.

3.1 Transcatheter Arterial Embolotherapy

3.1.1 General Principles

Pre-procedure arterial anatomy can be elucidated from prior CT or MR imaging of the abdomen and pelvis. Arterial phase high-resolution imaging is very helpful in procedure planning and significantly reduce time to cannulation of target vessels. It often precludes the need for non-selective aortic catheter angiography which reduces overall contrast and radiation exposure. Also, it helps in identification of important collaterals and non-target vessels for safe and effective embolization.

Arterial access may be obtained via femoral or radial approaches using ultrasound guidance and single wall arterial puncture. Vascular sheaths (4–5F) are usually inserted and should be connected to continuous pressure-infusion of saline to prevent clot formation in the sheath. For tortuous anatomy, long and pre-shaped guiding sheaths or catheters are helpful. We use combinations of 4F or 5F parent catheters (usually Cobra-2 or Simmons-1 shape) and high-flow microcatheters (2.7F to 2.0F) thus forming a triaxial system.

Access of the internal iliac artery is often easier from the contralateral femoral approach. However, in cases of marked atherosclerosis and tortuosity, an ipsilateral femoral approach may be easier. Some practitioners advocate bilateral femoral cross-over accesses with two simultaneous operators for speed and reduction of radiation dose. The transradial approach allows antegrade access to both internal iliac arteries and has gained significant popularity for prostatic and uterine embolization. However, the longer catheter and microcatheter lengths are required, and patient positioning can sometimes be challenging when cone-beam or angio-CT is to be performed in selected vessels.

The internal iliac artery has a variable branching pattern, but most commonly (about 75%) a bifurcation into anterior and posterior divisions (Pelage et al. 1999). The anterior division usually provides the relevant arterial visceral branches for the current topic.

Demonstration of target and important non-target vessels is essential in the pelvis to avoid major complications. Angiography should be performed using high-quality angiographic systems, using digital subtraction (DSA) as far as possible. We find the use of undiluted contrast to be more efficacious than diluted contrast in the demonstration of fine distal arterial vasculature. Contralateral anterior oblique (25–40°) view is often ideal for demonstrating the origins of the internal iliac and uterine arteries. The ipsilateral oblique (20–50°) with caudal (15°) angulation is complementary, particularly in variant anatomy.

Initial diagnostic angiography should be performed at high frame rates with exposure continued from the early arterial into the late venous phase. We often perform internal iliac arteriograms using an injection rate of 5 mL/s for 3 s (15 mL contrast), with DSA at 3 frames per second for 20 s. This allows detection of accumulated extravasated contrast after the intravascular contrast has cleared. The rate and volume of injection should obviously be calibrated in each vessel to prevent reflux. Bowel movement artifacts can be reduced with judicious administration of intravenous hyoscine or glucagon. In patients who are not fully able to cooperate, general anesthesia with paralytic agents should be considered for optimal breath-hold and suspension of movement.

3.1.2 Internal Iliac (Hypogastric) Artery Embolization

Internal iliac (hypogastric) artery embolization was described over 40 years ago in an illustrative case (Hald and Mygind 1974) of a 79-year-old male patient with bladder carcinoma who presented with severe vesical haemorrhage secondary to radiation cystitis. Treatment with electrocoagulation, instillation of EACA and intravesical pressure had failed, complicated by sepsis related to pressure treatment and the patient had required multiple hospital admissions with a total of 30 units of blood transfusion.

Hald and colleagues (Hald and Mygind 1974) initially performed unilateral (right) hypogastric artery embolization with autologous blood clot however bleeding recurred after a few days. Using a technique borrowed from the neurosurgical treatment of intracranial arteriovenous fistulas, they embolized the hypogastric artery with finely cut pieces of autologous muscle tissue (harvested from the patient's vastus lateralis muscle). This resulted in effective control of bleeding but transient tenderness and induration of the right (ipsilateral) gluteal region and posterior right thigh which they attributed to ischaemia. When angiography was performed because of recurrence of severe haemorrhage 6 months later, the authors noted continued occlusion of the embolized right hypogastric artery, but with distal revascularization from the contralateral hypogastric artery and the right external pudendal artery. The patient eventually required surgical urinary diversion.

Bilateral anterior division hypogastric artery coil embolization for advanced pelvic urological malignancies was described in a more recent report by Nabi et al. (2003). They treated three patients each with intractable haemorrhage due to advanced transitional cell carcinoma of the urinary bladder and advanced prostate adenocarcinoma who had failed other methods (including bladder irrigation and endoscopic treatment). Four of the 6 patients had recurred after palliative or radical radiotherapy, and two were too sick for transport to the radiotherapy unit. The authors reported complete control of bleeding after 1 session in 5 of 6 patients, and after two sessions in all patients. There were only relatively minor adverse effects of nausea/vomiting and fever, with no ischaemic complications. At follow-up (mean 22 months, range 10–60 months), no recurrence of haemorrhage was noted and no patient required further blood transfusion after embolization (Nabi et al. 2003).

Pisco et al. (1989) reported a large series of internal iliac artery embolization in 108 patients (76 female; age range 29–78) with uncontrollable haemorhage due to pelvic malignancies (urinary bladder, uterus, ovary, prostate), requiring 4–25 units of blood transfusion. Embolic material used was $2mm^3$ gelfoam particles in the first 20 cases, then PVA particles (250–590 μm). They reported complete bleeding control in 74 patients (69%) defined as absence of bleeding after at least 1 month from procedure, partial control in 23 patients (21%) defined as reduction of bleeding intensity and no control in 11 patients (10%). Post-embolization syndrome (nausea/vomiting, gluteal pain and fever) was reported in 65%. Major complications included contrast-induced transient acute tubular necrosis (n = 3); gastric ischaemia, skin necrosis associated with gluteal ischaemia and minor gluteal paresis (n = 1 each); and distal emboli requiring embolectomy (n = 2). Among 10 cases where reflux of embolic material was noted into the posterior division of hypogastric artery, gluteal ischaemia occurred in one case. Mortality at 6 months was 25% (27 patients) for the whole cohort, compared to 8% for patients in whom complete control of bleeding was obtained.

It is important to perform bilateral embolization with permanent agents even if tumour supply appears to be unilateral on angiography due to the rich collateral network (Pisco et al. 1989). But at the same time, essential to preserve distal perfusion to viscera, e.g. urinary bladder, vagina, penis and gluteal muscles to prevent debilitating complications from end organ ischaemia such as skin, muscle and bladder necrosis (Braf and Koontz 1977; Ali et al. 2014). Hence, only relatively proximal occlusion is advised (coils, large particles or gelfoam) to allow arteriolar and capillary reperfusion via pelvic collaterals.

3.1.3 Prostatic Artery Embolization (PAE)

Advances in catheter and guidewire design and imaging systems has allowed increasingly superselective catheterization of visceral arteries. PAE has been well described for control of prostatic haemorrhage in the palliative setting, in postoperative patients and in benign disease (BPH) (Carnevale and Antunes 2013). In the context of this chapter, PAE is performed even in the absence of active extravasation, unlike embolization in other scenarios (e.g. renal or bowel haemorrhage). The aim of embolization is complete

bilateral prostatic artery occlusion to reduce inflow perfusion pressure to the organ (Pereira et al. 2016; Rastinehad et al. 2008a; Prasad et al. 2009; Korkmaz et al. 2016; Chen et al. 2017). Unilateral PAE has a significant risk of recurrence due to contralateral collateral circulation; hence, bilateral embolization should be attempted in most cases.

Preoperative vascular imaging with CT or MR angiography is recommended to define the vascular anatomy. Super-selective catheterization of the prostatic arteries is important to avoid the potential complications of non-target embolization such as bladder necrosis, rectal ischaemia, gluteal ischaemia and Brown-Sequard syndrome (Pereira et al. 2016; Moreira et al. 2013; Teichgräber et al. 2018). Pre-procedure antibiotics (e.g. intravenous 400 mg ciprofloxacin) are given and continued (500 mg orally twice daily) for 7 days post procedure. A Foley catheter with balloon inflated with dilute (30%) iodinated contrast can be inserted to provide orientation to the gland for angiography and cone-beam CT (Carnevale and Antunes 2013).

Vascular access is usually obtained in the common femoral artery or radial artery, depending on patient factors and operator preference. Both of these have advantages and limitations which are discussed separately. Pelvic angiography is first performed with a pigtail catheter, followed by selective angiography of the internal iliac arteries, then super-selective prostatic and vesicular arteriography. The main prostatic artery is usually the second or third branch of the anterior division of the hypogastric artery. Important anatomic variations include common origin of the prostatic and superior vesical artery.

There is usually one main prostatic artery on either side (called the inferior vesical artery), but additional supply may be derived from the superior vesical, internal pudendal, obturator and middle rectal arteries (Carnevale and Antunes 2013). Bilateral cannulation can usually be performed via unilateral femoral access—a Cobra-2 or vertebral catheter can be used for the contralateral hypogastric artery while a reverse curve (Simmons I) catheter is used to cannulate the ipsilateral internal iliac artery, or alternatively, a Waltman loop can be used. In cases of marked vascular tortuosity, bilateral access may be helpful. Alternatively, brachial or radial access may be useful, but longer length catheters and microcatheters should be obtained for the procedure.

The main prostatic artery and accessory branches can be visualized with a 25–55° ipsilateral oblique view with 10–20° caudal angulation. In this view, the prostate branches are anterior and rectal branches are posteriorly located. In addition, the Foley catheter balloon provides an important landmark as the target structures are located immediately caudal to the balloon (Carnevale and Antunes 2013).

Once the microcatheter is placed in the main prostatic artery, angiography should be performed in ipsilateral and PA views to identify collateral vessels and contralateral prostate supply. Confirmation of microcatheter placement with cone-beam (Bagla et al. 2013) or angio-CT is recommended to avoid non-target injury. The microcatheter should ideally be placed as distal as possible, close to the origin of the intraprostatic branches of the main prostatic artery. If distal cannulation is not possible, embolization of important non-target branches using proximal short (2 or 3 mm) coils is suggested to protect these vessels. Subsequently, embolization is performed using calibrated particles (300–500 μm) (Carnevale and Antunes 2013; Goncalves et al. 2016) with technical end-point of stasis. Coil embolization of proximal non-target vessels may be employed to "protect" these vessels from distal particle embolization (Rastinehad et al. 2008b; Delgal et al. 2010).

Note however, that the vessel cannulation can be technically challenging in this patient population, contributed by age-related vascular tortuosity, atherosclerosis, radiation-induced vasculopathy and surgical or tumour-related vascular distortions (Korkmaz et al. 2016). Further, there is considerable anatomic variation in the vascular territory, particularly the origin of the inferior vesical artery which is an important non-target vessel that should be protected to avoid complications such as bladder wall necrosis (Pereira et al. 2016; Chen et al. 2017;

Appleton et al. 1988). Review of the arterial anatomy/variations and optimal imaging is essential to avoid complications, and the reader is referred to excellent manuscripts on the subject (Carnevale and Antunes 2013; Chen et al. 2017; Bagla et al. 2013; De Assis et al. 2015).

Technical success rates of prostatic artery embolization are reported in the range of 88–100%, with clinical success rates (defined as successful arrest of bleeding and improvements in haematocrit) ranging from 70 to 100% (Pereira et al. 2016; Korkmaz et al. 2016). Rebleeding is reported in the range of 15–28% over a follow-up period of 16–20 months (Pereira et al. 2016; Rastinehad et al. 2008b; Delgal et al. 2010), but there is evidence to suggest that repeat catheter directed therapy achieves high clinical success (Delgal et al. 2010).

3.1.4 Uterine Artery Embolization

Selective uterine artery embolization using gelfoam fragments was described by Brown et al. in 1979 for postpartum haemorrhage which was not responsive to surgical bilateral hypogastric artery ligation (Brown et al. 1979). Since then, UAE has become an integral part of management of intractable uterine bleeding.

The uterine artery usually arises as the first or second branch of the anterior division of the internal iliac artery and describes a characteristic tortuous "L-shape" with three segments: proximal inferolaterally directed descending segment, medially directed transverse segment and distal ascending segment coursing along the uterine sidewall (Salazar et al. 2009). The distal ascending segment gives off paired (anterior and posterior) arcuate arteries which anastomose with the contralateral branches. During embolization, the catheter or microcatheter should be advanced at least up to the transverse segment to avoid the branches to the cervix and vagina. Bilateral uterine artery embolization is performed under direct fluoroscopy to avoid reflux of embolic material. Temporary (gelfoam slurry) and permanent (PVA particles or microspheres) agents have been described with the latter preferred in tumour bleeding to avoid early recurrence.

Selective arterial embolization (SAE) of the massive vaginal haemorrhage was described by Field et al. (2016) in a series of 11 patients (of 1146 patients with genital tract malignancies). Embolization was performed using microspheres (300–700 μm and/or 500–900 μm) and coils or gelfoam in selected cases, together with adjuncts, e.g. vaginal packing and medical therapy. Vaginal bleeding ceased in all patients. Culprit arteries included the cervical branch of the uterine artery and the vaginal artery when active extravasation was seen on catheter angiography in about 50% of cases. Empiric embolization of the uterine arteries was performed when bleeding was not seen. The technique is similar to that described previously. Vaginal packing should be removed prior to angiography. Selective catheterization and angiography should be performed as far as possible. Embolization should begin with smaller range particles for more distal occlusion, then larger size particles. Coils should be used sparingly if at all to prevent occlusion of main vessels in the event of rebleeding occurring due to collateralization (Field et al. 2016).

3.1.5 Renal Artery Embolization

Renal cancer may present with intractable haematuria, renal obstruction and pain. Nephrectomy is usually performed as a definitive procedure even in palliation cases, but in some instances, advanced disease may preclude surgery. As renal cancer responds poorly to chemotherapy, palliative renal embolization is performed for symptom control (Niekamp et al. 2017). Embolic agents used include absolute ethanol, PVA particles and NBCA glue. Devascularization of the renal parenchyma can produce significant transient pain, which should be managed aggressively.

3.2 Bilateral Ureteric Embolization

This palliative urinary diversion technique is typically used in the management of urinary fistulae

(e.g. ureterovaginal, vesicovaginal or vesicocutaneous fistulae) and/or continuous urinary incontinence. However, it has also been described in the management of haematuria resulting from uretero-arterial fistulas, and it may have an adjunctive role in the palliation of haematuria from advanced bladder cancer or refractory haemorrhagic radiation cystitis (Yarlagadda et al. 2016). Removing the continuous fluid contact and urokinase may thus allow the formation of stable clot at the haemorrhagic site. Various techniques (Yarlagadda et al. 2016; Saad et al. 2013; Popuri and Zuckerman 2011; Guenther et al. 1979) have been described in the literature, using coils, Amplatzer plugs, glue, detachable balloons, sandwich techniques and "back-table" innovations but no conclusive data is available to recommend one technique over another. Long-term ureteric occlusion exploits urothelial hyperplasia and stricturing that results from chronic irritation, e.g. from coils or vascular plugs (or even stents). However, immediate success depends on near-complete luminal occlusion to prevent urinary passage.

Our preferred solution is to use type-I or II Amplatzer vascular plugs in combination with glue and coils in a "sandwich technique". A 7F, 35 cm braided sheath is inserted into the ureter via antegrade transrenal access and a 4F end-hole diagnostic catheter is advanced into the ureter. An 8–12 mm diameter plug is deployed in the ureter distal to the pelvic brim and 1–1.5 mL NBCA glue is injected directly into the plug interstices using a coaxial microcatheter. Fibred coils (e.g. 6–8 mm diameter 0.035″ Nester coils) are placed above the glue cast via the 4F catheter to provide a durable yet cost-effective option. Glue alone tends to fragment and recanalize in the ureter over time (Guenther et al. 1979) and requires a stable lattice in order to form a stable occlusive plug. The upper end of the glue cast also needs to be stabilized—using coils or another Amplatzer plug as described by Saad et al. (2013). Covered occlusive plugs, e.g. the microvascular plug may also be viable solutions in some cases, but are limited by their maximum size of 7 mm.

3.3 Percutaneous Thermal Ablation

RF electrocoagulation devices are long established in open and laparoscopic surgery for control of haemorrhage. Percutaneous image-guided thermal ablation of the haemorrhagic source (Neeman et al. 2005; Wood et al. 2001) is thus an attractive option as it potentially provides rapid minimally invasive option that directly targets abnormal tissue and avoids the use of iodinated contrast.

Neeman et al. (2005) reported four patients with tumour-related massive haematuria treated successfully with percutaneous RF ablation under conscious sedation. All patients had baseline renal impairment which precluded trans-arterial embolization in 3 of 4 patients. Underlying disease was metastatic renal cell carcinoma in 3 patients and melanoma metastasis to kidney in 1 patient. Multiple and prolonged ablations were performed in overlapping zones to treat the relatively large tumours (up to 7 cm) with palliative rather than curative intent. Ablation needle tips were placed several millimetres from the junction of tumour and collecting system, without entering the calyces. The authors hypothesized that this may eliminate the communication between tumour and collecting system. All patients were free of need for blood transfusion immediately after ablation although microscopic haematuria was still present in all patients. Two patients presented with one episode each of gross haematuria during 8-month follow-up which were self-limited. Impressively, renal function improved in all patients and the procedures clearly provided effective palliation.

3.4 Potential Complications and Limitations

The type of complication obviously depends on the treatment chosen and the underlying disease causing the bleeding. These can be divided into general and procedure specific. General

complications include intravenous contrast-related adverse effects such as renal dysfunction and allergy, post-embolization syndrome such as pain, fever and leukocytosis and rare delayed effects of radiation exposure.

Procedure-specific complications include puncture-site problems (haematoma/pseudoaneurysm formation), non-target embolization, infection and recurrence of bleeding.

Non-target embolization is a major concern for embolotherapy in the pelvis, contributed by complex/variant anatomy. Potential complications may include lower limb ischaemia from reflux into the external iliac artery, gluteal muscle ischaemia, visceral infarction (e.g. urinary bladder necrosis (Ali et al. 2014), rectal ischaemia (Moreira et al. 2013)), ovarian failure, sciatic/femoral nerve injury (Hare and Holland 1983) and impotence in males. The risk is greater when using small particles and with more proximal injections. For non-selective internal iliac artery embolization, gelfoam particles are hence recommended due to their relatively large particle size (gelfoam powder should not be used as it is linked to bladder necrosis).

With ablative procedures, the aim should be to eliminate bleeding without attempting to destroy all portions of the tumour as this may increase the risk of complications, such as urine leak, injury to adjacent bowel, infection or haemorrhage. Post-ablation, aggressive bladder washout is also recommended to prevent bladder outlet obstruction from sloughed tissue or blood clots (Neeman et al. 2005).

4 Conclusion

Genitourinary bleeding can potentially cause severe morbidity as described in this chapter, yet optimal treatments, e.g. surgery and radial radiotherapy are limited or impossible in this debilitated population. Interventional radiologic techniques may provide cost-effective minimally invasive solutions and should be considered early in a multidisciplinary management plan.

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Bleeding Solutions in Lung

Nanda Venkatanarasimha,
Karthikeyan Damodharan, Robert Chun Chen,
Kristen Alexa Lee, and Sivanathan Chandramohan

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1 Introduction

Hemoptysis is not an uncommon symptom in patients with underlying broncho-pulmonary malignancy, and occurs in about 30% of patients (Hirshberg et al. 1997) and in 10% it can be massive and in 3% fatal (Park et al. 2007). Without treatment, severe hemoptysis is associated with a mortality rate exceeding 50% (Witt et al. 2000). Bleeding can be related to local tumor invasion, tumor angiogenesis, systemic effects of the cancer like thrombocytopenia and coagulopathy, chemotherapy, or iatrogenic related to percutaneous or endoscopic interventions. Existing bleeds can be exacerbated by medications such as bevacizumab, anticoagulants, antiplatelets, and

N. Venkatanarasimha · K. Damodharan · R. C. Chen
K. A. Lee · S. Chandramohan (✉)
Department of Vascular and Interventional Radiology, Singapore General Hospital, Singapore, Singapore
e-mail: sivanathan.chandramohan@singhealth.com.sg

© Springer Nature Switzerland AG 2021

P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_20

non-steroidal anti-inflammatory drugs. Patients may present with small volume bleeding, episodic major bleeding, or with acute catastrophic bleeding resulting in hemorrhagic shock or severe respiratory distress/failure and ultimately death. Given the complex patient population, multifactorial etiologies, and the variety of treatment modalities involved, palliative management of broncho-pulmonary bleeding has been challenging. Surgery is the definitive treatment for hemoptysis, but the underlying frailty makes these patients unsuitable for any aggressive cardiothoracic surgical interventions. Hence, percutaneous and/or endovascular management is frequently considered a first-line palliative option in these medically precarious patients. Some of the other treatment options include external beam radiotherapy, airway stenting, and endobronchial laser ablation.

Fig. 1 47-year-old male with known melanoma presented with hemoptysis. CT coronal reformat demonstrates the enhancing tracheal metastasis causing significant luminal compromise (arrow)

2 Etiology

Typically, there are many causes and often several confounding factors leading to bleeding within the broncho-pulmonary-pleural complex in patients with thoracic malignancy. Some of these are directly the consequence of tumor within the trachea-bronchial tree (Fig. 1), tumor erosion of a proximal vessel (Fig. 2) resulting in a pseudoaneurysm or large venous collateral rupture in patients with superior vena caval obstruction. Indirect causes include neovascularization from growth factors, thrombocytopenia from bone marrow invasion or coagulopathy. Iatrogenic causes include the consequence of diagnostic/therapeutic interventions including newer immunotherapeutic agents like Bevacizumab. Bevacizumab is reported to delay surgical wound healing and also increases the risk of arterial injury and aneurysm formation (Fig. 3). Risk factors for severe hemoptysis in patients with lung cancer includes central location of the tumor, tumor cavitation, hypervascular primary/secondary tumors, and antiangiogenic treatment (Goto et al. 2016). Patients with malignancy can present with hemoptysis related to chronic inflammatory causes like tuberculosis, aspergillosis, bronchiectasis, and chronic bronchiectasis. Non-malignant, advanced disease like cystic fibrosis and congenital cardio-pulmonary diseases can present with severe hemoptysis, and is some cases it is recurrent. Some of the common and uncommon causes of hemoptysis in the palliative setting is summarized in Table 1.

3 Anatomical Considerations

A thorough knowledge of vascular anatomy is important when endovascular intervention is contemplated. Anatomical variants are not uncommon. The bronchial arteries are responsible for more than 90% of hemoptysis, and frequently are hypertrophied (Yoon et al. 2002). However, non-bronchial systemic arteries are often the source of hemoptysis when the malignancy invades the

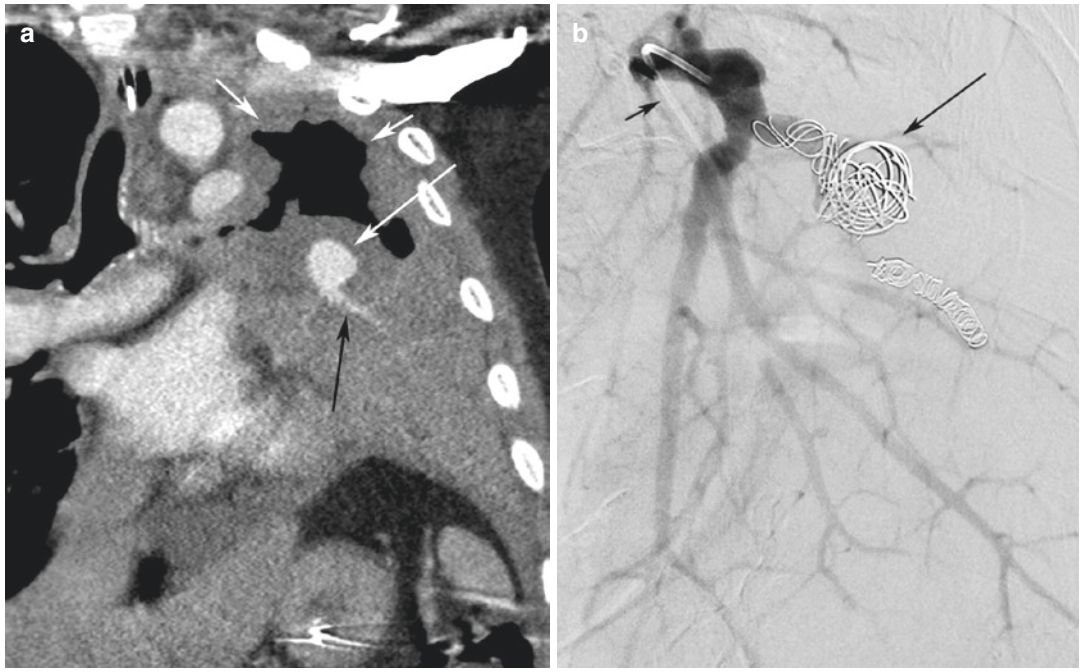

Fig. 2 65-year-old male with known advanced left bronchogenic (squamous cell) carcinoma presented with massive hemoptysis. (**a**) CT coronal reformat shows the pseudoaneurysm (long arrow) supplied by a pulmonary artery branch (black arrow) within the cavitated tumor (short arrows). (**b**) Post-embolization pulmonary angiography with catheter in the left pulmonary artery (short arrow) shows successful exclusion of (long arrow) the pseudoaneurysm

pleura or the chest wall, large hypervascular tumors, and also when hemoptysis is related to chronic inflammatory and congenital heart diseases. The non-bronchial systemic arteries that commonly parasitize include internal mammary, internal thoracic, inferior phrenic, thyrocervical trunk, and intercostal arteries. Iatrogenic causes of bleeding, related to percutaneous interventions of pleural or pulmonary tumors can cause bleeding from pulmonary, bronchial (Fig. 4), or an intercostal artery (Fig. 5).

Bronchial arteries arise from the descending thoracic aorta at the level of the third through eighth thoracic vertebrae, most frequently at T5–T6 (Roberts 1990; Stoll and Bettmann 1988). In 20%, the bronchial arteries have an aberrant origin and may arise from the subclavian, brachiocephalic, internal mammary, or from the abdominal aorta (Stoll and Bettmann 1988; Uflacker et al. 1985). At least ten different patterns of bronchial artery anatomy have been recognized. The most consistently identified artery (seen in 80%) is the right intercosto-bronchial trunk.

Anastomoses between the bronchial arteries and tributaries of the pulmonary veins are demonstrated in normal lungs at postmortem; these anastomoses permit drainage of bronchial arterial blood into the left heart. During malignant process or chronic inflammatory pulmonary conditions, the volume of such communications may increase (Fig. 6), and these are relevant to the choice of embolic agents used, and thus, prevent catastrophic complications like stroke or myocardial infarction from inadvertent embolization. Enlargement and marked tortuosity of bronchial arteries, and increased arterial blood flow have

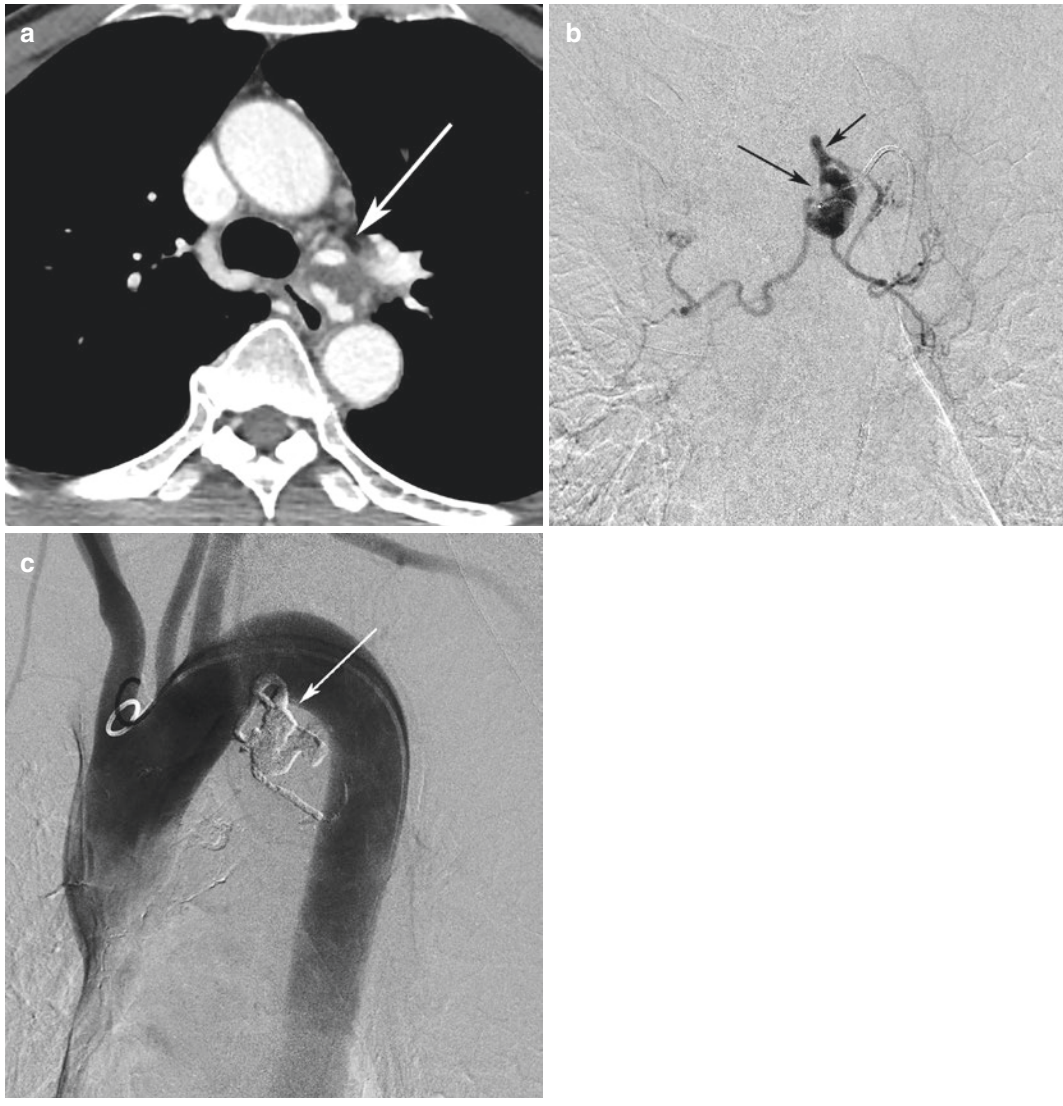

Fig. 3 60-year-old male patient with metastatic colon cancer treated with Bevacizumab was noted to have bronchial artery aneurysm. (**a**) Axial CT angiogram shows a 1.3 cm bronchial artery aneurysm with partial thrombosis. (**b**) Selective angiography performed via 2.2F microcatheter advanced coaxially via a reverse curve catheter shows the large aneurysm (long arrow) arising from the proximal common bronchial artery (short arrow). (**c**) Completion aortogram after embolization with 20% glue admixed with Lipiodol shows an occlusive glue cast (arrow) and non-filling of the aneurysm. (**IMAGE courtesy: Dr Apoorva Gogna**)

been observed. In these circumstances, new collaterals from the bronchial arteries or from other intrathoracic systemic arteries may develop. These pathological changes can account for an increased risk of bleeding.

Significant bleeding from pulmonary arterial or pulmonary venous involvement is relatively uncommon and is typically from direct tumor invasion or due to significant thromboembolic process within these vessels.

Table 1 Causes of hemoptysis in palliative situations

Direct tumor-related:
Vessel erosion/invasion
Tumor rupture (Hypervascular metastasis)
SVC obstruction (rupture of collaterals)
Tracheo-bronchial hypervascular metastasis
Indirect tumor-related:
Coagulopathy
Bone metastasis resulting bone marrow suppression
Paraneoplastic (thrombotic microangiopathy and vasculitis)
Disseminated intravascular coagulation
Macrophage activation syndrome
Infection:
Pulmonary tuberculosis (including Rasmussen aneurysm)
Fungal (including aspergillosis)
Lung abscess
Iatrogenic:
Chemotherapy and immunotherapy
Anticoagulants and antiplatelets
Post-operative pseudoaneurysm
Post-biopsy (percutaneous/bronchoscopy)
Post-radiotherapy (fragile vascular bed)

4 Solutions

Approximately 20% of patients with lung cancer will experience hemoptysis at some point during their course, but only 3% of patients will present with massive hemoptysis. Up to 80% of patients with massive hemoptysis due to malignancy have history of small sentinel bleeding episodes during the prior weeks. The presence of large, centrally located tumors with cavitation and especially squamous cell carcinoma is associated with massive hemoptysis. Timely management is paramount as every minute lost, equals more alveoli flooded with blood that can further compromise pulmonary function.

A multimodality team approach involving critical care pulmonary specialist, thoracic surgeons, and interventional radiologist is the key to managing these critically ill patients. The initial step in the management of significant hemoptysis should focus on patient stabilization. Establishing a definitive airway is the most important step. Moreover, protection of non-bleeding lung is vital and this can be achieved, initially, with simple common-sense steps like turning the patient to the bleeding side. This ensures that the blood is isolated to the bleeding lung due to gravity, and the non-bleeding side remains intact and fully aerated. Endotracheal intubation (ETT) is most easily available option to secure airway.

Any concurrent bleeding disorders should be corrected emergently and also, fluid/blood replacement to ensure hemodynamic stability. Anticoagulants and antiplatelet medication should be withheld.

4.1 Diagnostic Solutions

A thorough clinical history and physical examination provide clues to the underlying pathology and possibly the location of bleeding. Initial evaluation includes laboratory analysis which includes full blood count, coagulation profile, blood grouping/cross-matching, and renal function tests.

Bronchoscopy is useful in identifying the site of bleeding and is often requested prior to interventions/embolization. Bronchoscopy is valuable if the site of bleeding is inconclusive on clinical examination and on imaging, in patients presenting for the first time with hemoptysis, and in the presence of recurrent bleeding following embolization or surgery. However, it has limited use in the presence of massive hemoptysis, as aspirated blood makes it difficult to locate the bleeding site. The overall accuracy of bronchoscopy in evaluating patients with hemoptysis reaches 40–50%, but it falls to 0–31% in patients with normal chest radiograph (Yoon et al. 2002). In patients not requiring bronchoscopy for airway management, CT is highly informative in guiding further interventions like embolization (Hsiao et al. 2001).

CT provides excellent details regarding the presence, extent, location, and type of lung pathology. Also, it is noninvasive, poses less potential risk compared with bronchoscopy and provides essential information for therapy planning. CT is comparable to bronchoscopy for identifying the site of bleeding (70% *vs.* 73%, respectively); however, CT has been found to be more efficient than bronchoscopy in identifying

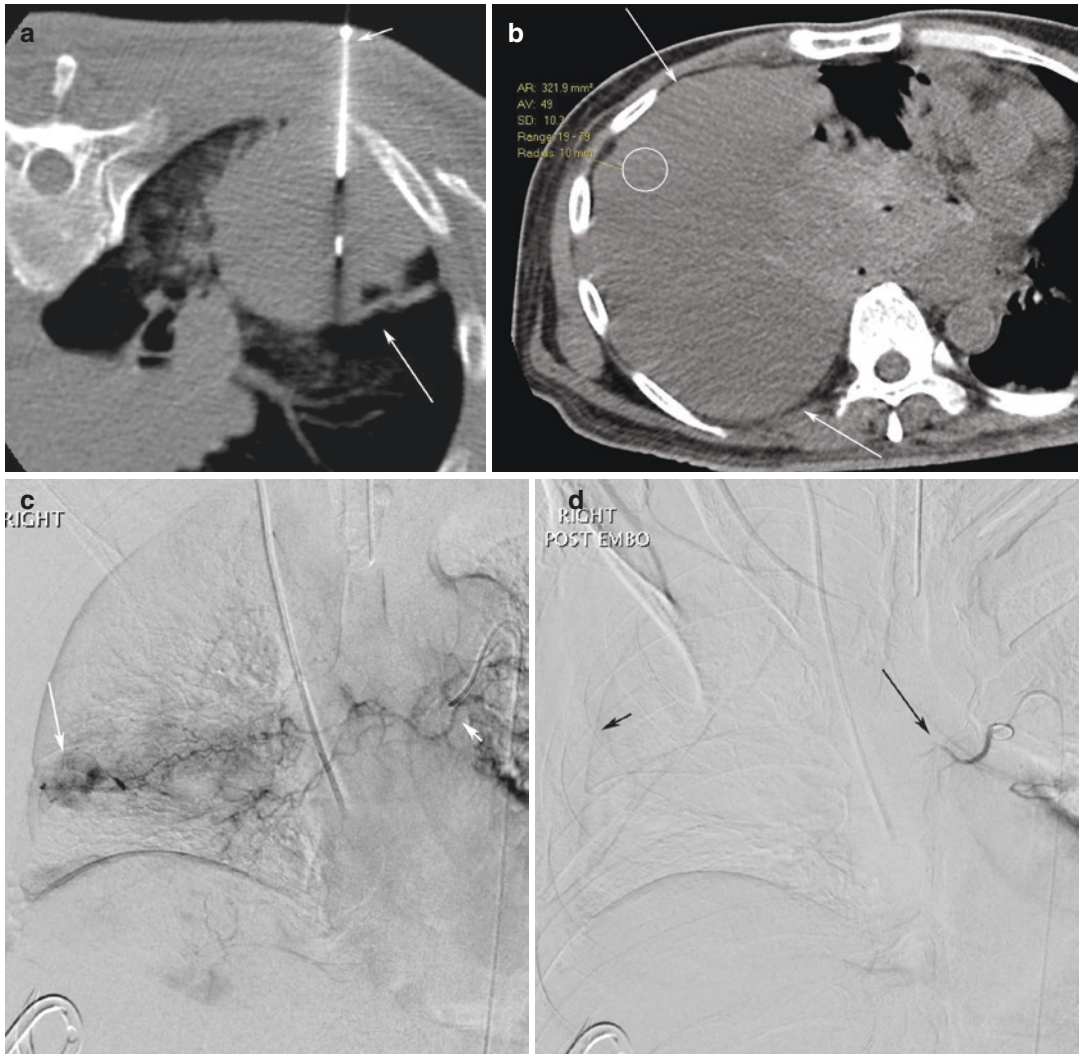

Fig. 4 63-year-old male developed worsening hemoptysis and massive hemothorax 4 h after percutaneous biopsy of a suspected right lower lobe pulmonary tumor. (**a**) CT-guided biopsy of the right lower lobe mass (long arrow) with an 18G (semi-automatic needle (short arrow) is shown. (**b**) Unenhanced CT thorax shows a massive right hemothorax (arrows). (**c**) Right bronchial artery (short arrow) angiography shows active extravasation (long arrow) from a peripheral branch. (**d**) Completion angiography after embolization of the vessel with 355–500 micron PVA particles shows near complete occlusion of the vessel (long arrow). Note the large hemothorax (short arrow)

the cause of bleeding (77% *vs.* 8%, respectively, $P < 0.001$) (Revel et al. 2002). Several studies compare CT with bronchoscopy, and it has been demonstrated that in a study of 40 cases of hemoptysis with normal bronchoscopy, abnormalities were seen in 50% of patients on subsequent chest CT scan. Some suggest that CT can replace bronchoscopy as a first-line investigational approach in patients with massive hemoptysis because of its higher diagnostic yield (Khalil et al. 2007), while others advocate it as complementary to fiber optic bronchoscopy for bleeding site identification (Revel et al. 2002).

The origin and course of the bronchial arteries and the involvement of non-bronchial systemic arteries can be visualized on thin-section

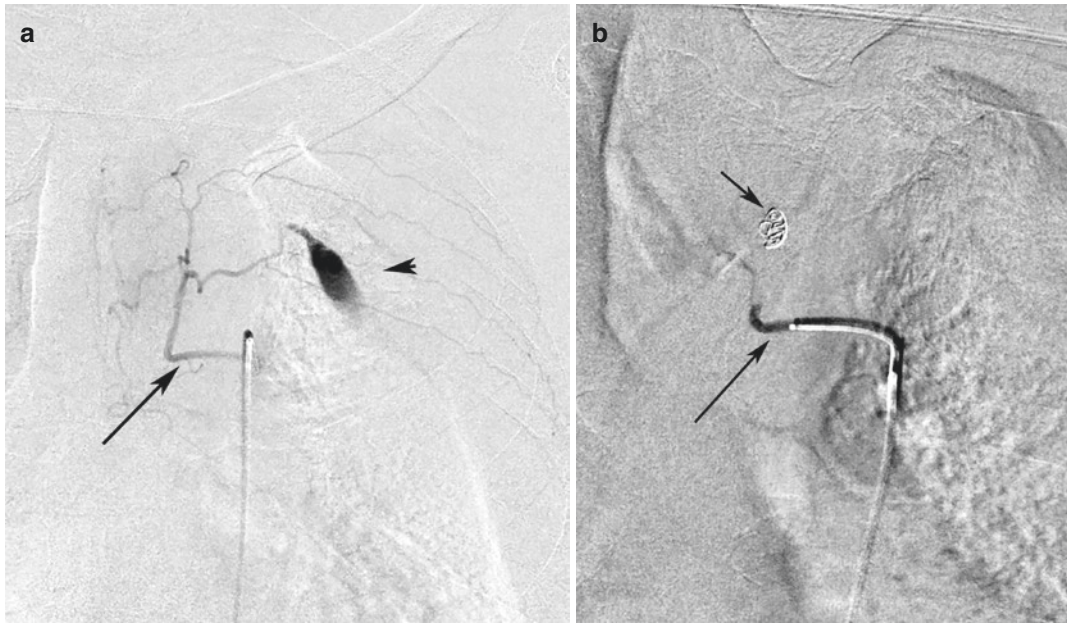

Fig. 5 60-year-old male developed worsening hemothorax immediately after percutaneous biopsy of a suspected left lobe pulmonary tumor. (**a**) Superselective cannulation of the left intercostal artery (long arrow) showed a pseudoaneurysm (arrowhead) with active bleeding from a small branch. (**b**) The culprit vessel (long arrow) was successfully coil embolized (short arrow) resulting in hemostasis

contrast-enhanced CT. This is useful for planning optimal intraprocedural C-arm orientation and may aid in more rapid selective catheterization of the involved arteries during angiography. Furthermore, the three-dimensional reconstruction can facilitate vessel mapping that can be used as a road-map for endovascular interventions.

The main disadvantages of CT are radiation risk, the need for potentially nephrotoxic contrast agents, and potential time delays in obtaining a CT study.

4.2 Treatment Solutions

A combination of noninvasive and invasive management strategies is employed to manage hemoptysis. These include systemic treatment (correction of coagulopathy, terlipressin, etc.), bronchoscopy directed (aspiration of blood, local instillation of cold saline lavage, and local vasoconstrictor agents such as epinephrine, tranexamic acid, or fibrinogen–thrombin combinations, endobronchial balloon tamponade, endotracheal intubation to protect the uninvolved lung, endobronchial tumor ablation) (Sakr and Dutau 2010), interventional radiology (embolization, stenting, percutaneous ablation), external radiotherapy, and surgical options (like lobectomy) after initial stabilization. The rest of this book chapter will focus on interventional radiology treatment options in managing hemoptysis.

Interventional radiology is increasingly considered as the first line of treatment in patients presenting with severe hemoptysis and bronchial artery embolization (BAE) is shown to achieve bleeding cessation in up to 80% of patients (Razazi et al. 2015; Wang et al. 2009). A variety of endovascular and percutaneous interventional radiology treatment options are available for managing patients with hemoptysis depending on the cause, extent and site of bleeding, and patient's hemodynamic status.

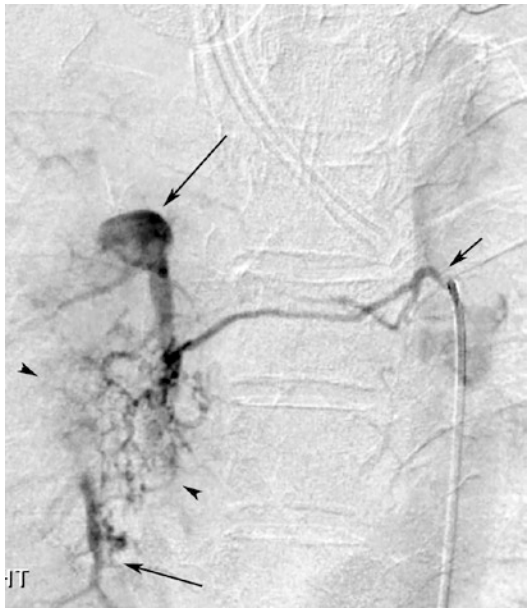

Fig. 6 57-year-old female with known lung squamous cell carcinoma treated with chemoradiation present severe hemoptysis. Selective right bronchial artery angiogram (short arrow) shows significant communication between the small arterial branches and pulmonary veins (long arrows). Also note the contrast staining (arrowheads) of the tumor and abnormal lung

5 Embolization

5.1 Bronchial Artery Embolization

BAE was first introduced in 1974 and is now widely used and often considered as first-line treatment in patients with massive hemoptysis after initial stabilization (Chen et al. 2014; Fernando et al. 1998; Fruchter et al. 2015).

The success rate of BAE ranges from 60 to 90% (Chen et al. 2014). In a study of 52 patients treated by BAE, Fruchter et al. reported an immediate success rate of 92% (48/52) within the first 24 h (Fruchter et al. 2015). Forty-five patients survived beyond 24 h and recurrent bleeding did not occur in 19 (42.2%) during a median follow-up period of 60 months (range, 6–130 months). Bleeding recurred in 26 (57.7%); within 30 days in 15 (33.3%) and after 1 month in the other 11 (24.4%). The average time to onset of early and late repeat bleeding was 2 and 506 days, respectively. Idiopathic bronchiectasis and lung cancer were associated with a high likelihood of late bleeding recurrence (Fernando et al. 1998). Re-bleeding can occur depending on the etiology of the bleed and may warrant repeat BAE. Recurrence is particularly noted in diseases such as TB, aspergilloma, and malignant lesions (Fig. 7) (Chun et al. 2010).

A thoracic aortography prior to selective bronchial artery angiogram can be very useful in identifying the origin, number, and course of the bronchial and non-bronchial systemic arteries. Selective catheterization of the bronchial arteries can be achieved with various catheter configurations. Digital subtraction angiography is highly useful in identifying the spinal arteries, as is correct anatomical positioning of the patient. The latter allows for rapid identification of the spinal arteries as they course over the center of the spine and demonstrate the classic "hair-pin" configuration. A low-osmolar contrast material is recommended for bronchial and intercostal angiography, as the use of high-osmolar contrast material is implicated as one of the causes of spinal ischemia (Kalva 2009). Active extravasation of contrast is seen in only 10–15% of all cases of hemoptysis. Lesions considered in lieu of active extravasation of contrast are bronchial arterial hypertrophy and tortuosity, hypervascularity, aneurysm formation, and arteriovenous malformations. Normal bronchial arterial appearance may be seen in up to 20% of cases. Tumors may demonstrate localized hypervascularity and staining of the tumor.

After identifying an abnormal bronchial/non-bronchial systemic artery, a suitably sized microcatheter is introduced coaxially through the parent catheter and embolized.

Polyvinyl alcohol particles (PVA) is commonly used in our center. Some use gelatin sponge with satisfactory results. The particles should be appropriately sized to prevent these materials from crossing into the pulmonary arteries or veins via shunts. By and large, particles size larger than or equal to 300 microns are used. Small particles increase the risk of bronchial and esophageal necrosis and inadvertent embolization of spinal arteries. In the presence of significant shunts, larger size particles, or gel foam torpedoes can be used. Embolization coils are

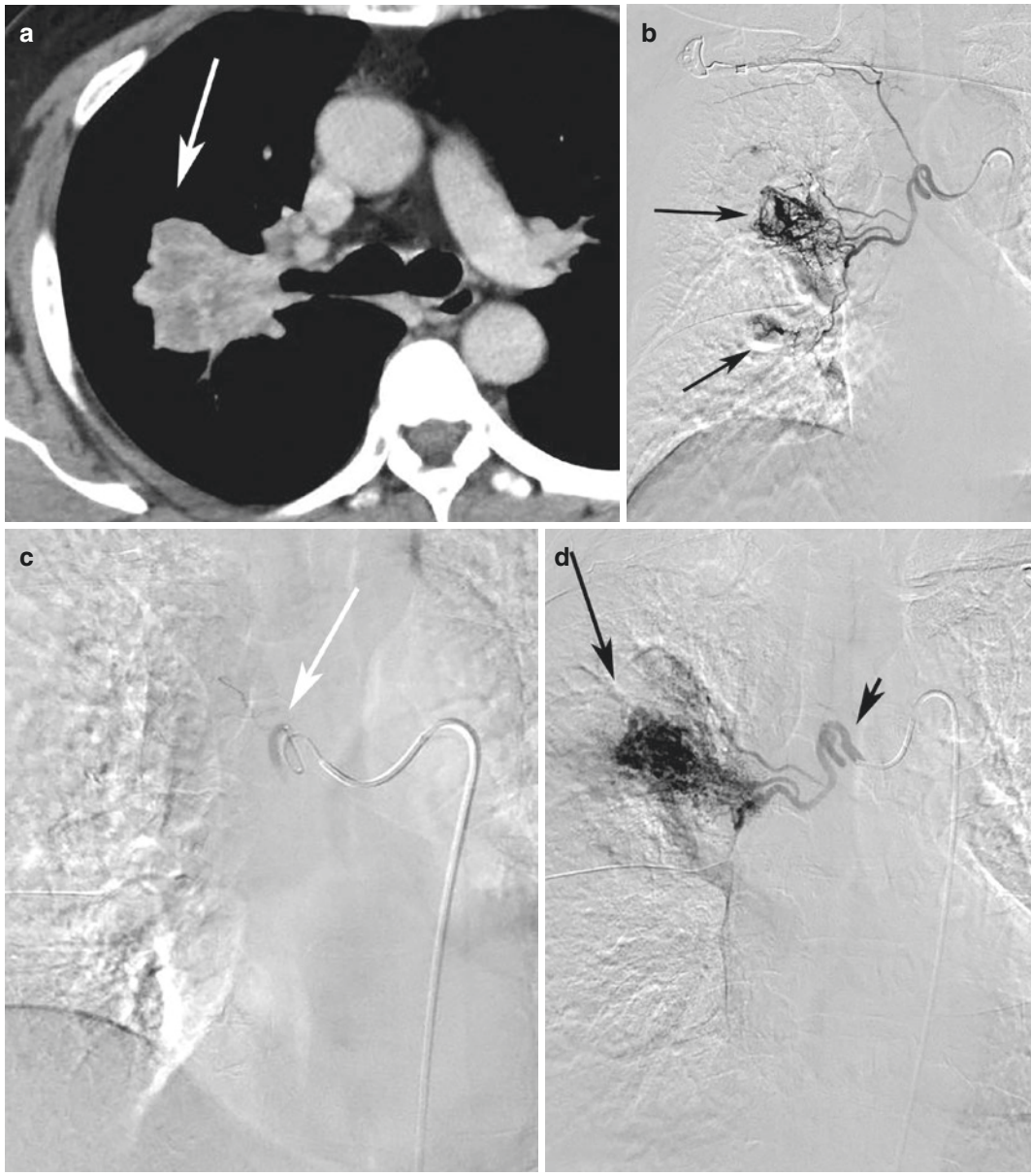

Fig. 7 61-year-old male with known metastatic renal cell carcinoma presented with massive hemoptysis. (**a**). Axial CT thorax shows a hypervascular right lung metastasis centrally. (**b**). Angiogram of the intercosto-bronchial trunk shows hyperenhancing metastases (arrows) supplied by the right bronchial artery. (**c**) Completion angiogram shows non-enhancement of the tumor and near complete occlusion of the right bronchial artery (arrow) after embolization with 355–500 micron PVA particles. (**d**) Repeat bronchial artery angiogram for recurrent hemoptysis 15 months later shows recanalized bronchial artery (short arrow) supplying the enlarged enhancing metastasis (long arrow). (**IMAGE COURTESY: Dr Andrew Tan**)

usually preferred for occlusion of proximal bronchial artery aneurysms and for embolization of abnormal communications between bronchial and systemic arteries to prevent non-target embolization. However, routine use of coils for proximal bronchial arteries is discouraged as it precludes further embolization procedures for recurrent hemoptysis. Liquid embolic agents like

N-butyl cyanoacrylate (glue) should be used with extreme caution and is challenging for experienced interventionist as the margin for error is minimal in this territory.

Complications of BAE include self-limiting chest pain, self-limiting dysphagia from non-target embolization to the esophagus, and transverse myelitis from non-target embolization to the spinal artery (Sharma et al. 2015). Rare complications include cortical blindness, tracheoesophageal fistula from esophageal ischemia, bronchial stenosis and necrosis from bronchial wall ischemia and pulmonary infarction (Deffebach et al. 1987).

5.2 Non-bronchial Systemic Artery Embolization

As discussed earlier, non-bronchial systemic artery supply is typically encountered when the disease process invades/involves the pleura and chest wall.

Technical success of bronchial and non-bronchial systemic arteries embolization is reported to be more than 90%. However, immediate clinical success in controlling bleeding is achieved in only 75–90% (Stoll and Bettmann 1988). Failure to stop bleeding may be due to technical difficulty in cannulating the bronchial arteries, failure to identify and embolize the culprit vessels.

5.3 Pulmonary Artery Embolization

The pulmonary arteries are responsible for less than 10% of patients presenting with hemoptysis. There are typically due to pseudoaneurysm from tumor erosion (Fig. 2) of the pulmonary artery (Gomez-Jorge and Mitchell 1999) or related to associated infective process like cavitary tuberculosis resulting in Rasmussen aneurysm (Fig. 8). Rasmussen aneurysm, which results from the destruction of the media in segmental pulmonary arteries by granulation tissue (Ghaye and Dondelinger 2001). Because of the risk of pseudoaneurysm enlargement and rupture, which leads to death in approximately 50% of patients, prompt therapy is warranted (Ghaye and Dondelinger 2001).

Endovascular technique is often considered as the first-line treatment for pulmonary artery pseudoaneurysms. A long sheath within the pulmonary artery is advisable as it provides stability while performing complex stenting or embolization.

It has been shown that transcatheter embolization can be safely and effectively performed with coils (Fig. 2) (Deshmukh et al. 2003), detachable balloons (Renie et al. 1982), Amplatzer plugs (Chellamuthu and Bottomley 2012), or liquid embolic agents like glue (Khalil et al. 2015). The choice of embolic materials depends on the size, location, and neck width of the pseudoaneurysm.

Occasionally, a pulmonary arteriogram may fail to demonstrate the pseudoaneurysm or its feeding artery because of a peripheral location, a vascular flap acting as a valve, or a thrombus formation (Khalil et al. 2015). When an endovascular approach is not feasible or failed, direct percutaneous embolization may be an alternate option. Hovis et al. reported a case of pulmonary artery pseudoaneurysm successfully treated by percutaneous injection of thrombin under fluoroscopic and sonographic guidance after failed transcatheter embolization (Hovis and Zeni Jr 2006). Similarly, direct percutaneous injection of *N*-butyl cyanoacrylate for successful management of a pulmonary artery pseudoaneurysm under CT/fluoroscopic guidance (Fig. 9) can be safely performed (David et al. 2017).

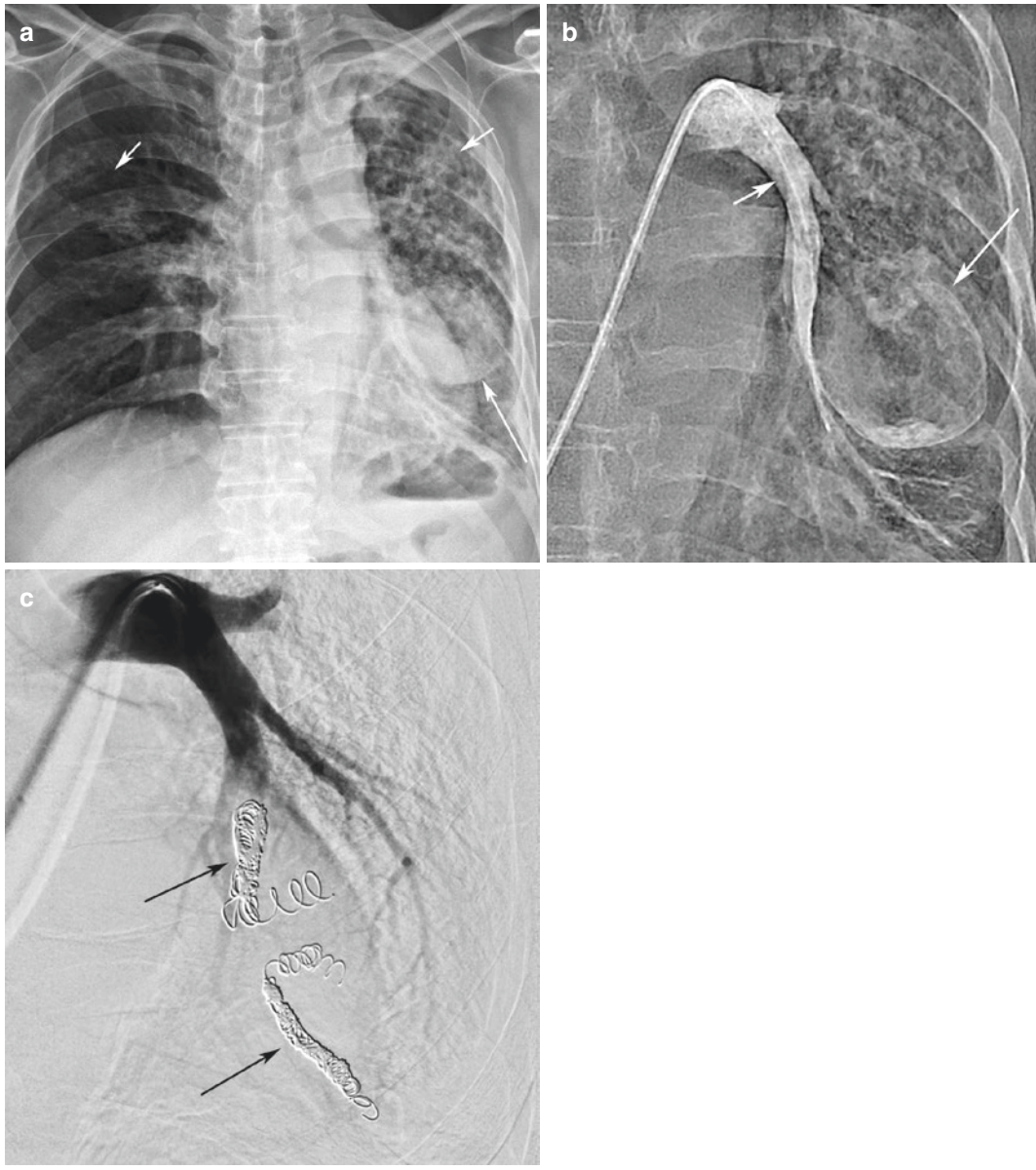

Fig. 8 55-year-old male immunosuppressed patient with newly diagnosed pulmonary tuberculosis presented with massive hemoptysis. (**a**). Chest radiograph shows a large cavitated mass in the left lower lung (long arrow) and extensive bilateral nodular tree-in-bud pattern (short arrows) involving both lungs. (**b**) Pulmonary angiography via the long sheath in the main pulmonary artery demonstrates a large pseudoaneurysm consistent with a Rasmussen's aneurysm (long arrow) responsible for the hemoptysis. Note a microcatheter (short arrow) in the left lower lobe pulmonary artery (**c**). The feeding arteries were coil embolized (arrows) and the pseudoaneurysm was successfully excluded resulting in hemostasis. (**IMAGE COURTESY: Dr Ankur Patel**)

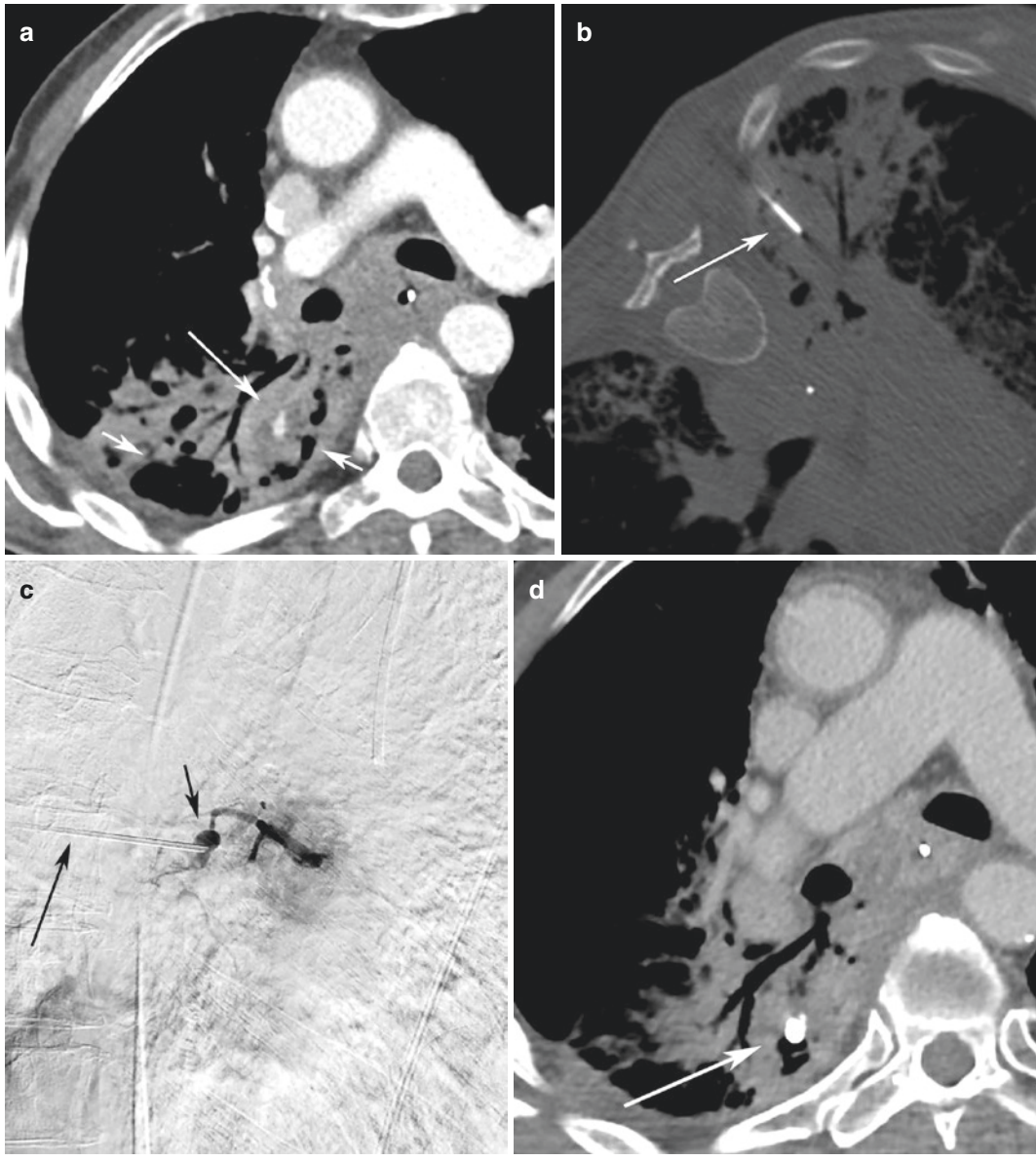

Fig. 9 58-year-old male patient with known squamous cell lung cancer treated with palliative chemoradiation presented with fever and worsening hemoptysis. (**a**) Axial CT pulmonary angiogram shows a small pseudoaneurysm (long arrow) arising from the superior segmental branch of the right lower lobe pulmonary artery. Note associated post-obstructive pneumonitis from the obstructing central tumor and cavities related to associated lung abscesses (short arrows). (**b**). Percutaneous embolization was performed in a hybrid angio-CT suite. Under intermittent CT guidance, a 21G needle (arrow) was advanced into the pseudoaneurysm. (**c**). Subsequently, an angiogram was performed via the Chiba needle, which shows the pseudoaneurysm fed by a small pulmonary artery branch. The aneurysm was injected with 1 mL of 50% glue (mixed with Lipiodol) resulting in hemostasis. (**d**). CT angiography performed 2 months later shows the glue cast in the previously seen pseudoaneurysm. (**IMAGE COURTESY: Dr Chow Wei Too**)

6 Stenting

6.1 Pulmonary Artery Stenting

The use of stent graft in the pulmonary artery could exclude the pseudoaneurysm with preservation of the distal flow (Fig. 10). A stent graft may be a safer alternative when embolization of a wide-mouthed pulmonary aneurysm is challenging or when perfusion distal to the aneurysm is desirable because of limited pulmonary reserve. The stent should be appropriately sized to account

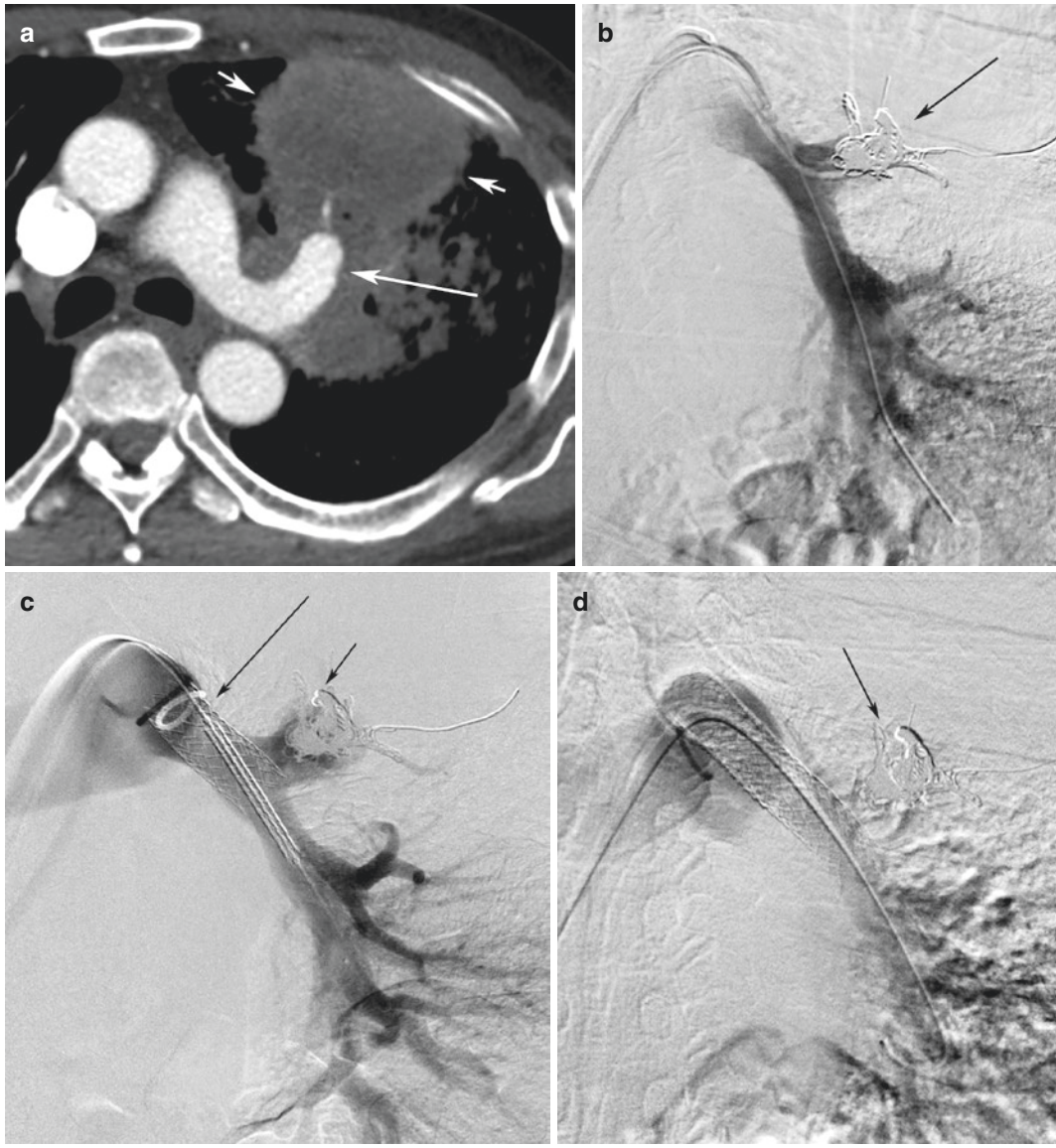

Fig. 10 68-year-old male patient with known metastatic lung adenocarcinoma treated with palliative chemoradiation presented with massive hemoptysis. (**a**) Axial CT pulmonary angiogram shows a large pseudoaneurysm (long arrow) due to erosion of the proximal left pulmonary artery by the large tumor (short arrows). (**b**) Pulmonary angiogram after coil embolization shows satisfactory results with no further opacification of the pseudoaneurysm (arrow). (**c**) Follow-up CT showed recanalization and enlargement of the pseudoaneurysm. Initial covered stent-graft deployed (Long arrow) into the left pulmonary artery was short and a second stent is being deployed. Note the filling of the pseudoaneurysm with contrast (short arrow) (**d**). After the extension of the stent graft further distally results in successful exclusion of the pseudoaneurysm (arrow)

for the distal tapering of the pulmonary artery. An undersized stent can result in distal stent migration or type I endoleak.

6.2 Tracheo-Bronchial Tree Stenting

Airway stents are traditionally used in the palliation of lung cancer to maintain patency of reopened airways, to secure patency of a collapsed or extrinsically compressed central airway, and to occlude fistulas. There are few anecdotal case reports that have described stenting of airways for managing severe hemoptysis (Chung et al. 2010) when other traditional techniques like embolization is not feasible. Stenting of the airways not only facilitates successful tamponade and isolation of bleeding source but also allows for maintaining the patency of the airway. Potential complications include stent migration, stent fracture, and loss of normal clearance of secretions resulting in infection and obstruction (Zakaluzny et al. 2003).

7 Ablation

Image-guided tumor ablation for lung malignancies has emerged as a treatment modality for medically inoperable patients. Image-guided percutaneous lung tumor ablation is a minimally invasive procedure that has an acceptable safety profile and minimal impact on lung function (Dupuy et al. 2000). This is important for patients with poor pulmonary and/or cardiac functions or with multiple comorbidities, which prevent them from undergoing surgery, chemotherapy, and radiation therapy. Baisi A et al. reported a case of percutaneous radiofrequency ablation of an inoperable large lung tumor that presented with severe hemoptysis (Baisi et al. 2010). Percutaneous thermal ablation may be useful in the management of hemoptysis complicating pulmonary malignancy that is not suitable for other minimally invasive procedures like endobronchial coagulation or endovascular embolization.

8 Conclusion

Bleeding is a common complication in patients with advanced cancer, but the approach to prevention and treatment will vary substantially based on the type and site of bleeding. Unfortunately, literature is limited for palliative treatment of bleeding in advanced cancer, including few prospective studies, a lack of consistent endpoints, and no randomized trials. Therapeutic intervention for bleeding in palliative settings should start by establishing goals of care, and treatment choice should be guided by patient preferences, life expectancy, and quality of life.

Furthermore, a close collaboration between interventional radiologists, pulmonologists, oncologists, anaesthesiologists, and critical care physicians is mandatory for optimal management in patients with full therapeutic options. Nowadays, percutaneous interventional radiology techniques for emergent treatment of hemoptysis is well established, well tolerated, effective, minimally invasive, and a safe alternative to open surgery. Lastly, interventional radiology is increasing and used as a first-line treatment option for palliation in these otherwise very sick patients.

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Bleeding Solutions in Hepatobiliary Pancreatic Systems

Seung Wook Ryu and Uei Pua

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Abstract

Non-traumatic haemorrhage from hepatobiliary and pancreatic system is not common. Particularly in the palliative setting, the interventionalist plays an important role in controlling the bleeding source. In this chapter, endovascular embolization techniques for hepatobiliary and pancreatic systems are discussed, with the main focus on the palliative care setting.

Abbreviations

AVP	Amplatzer vascular plug
CT	Computed tomography
DSA	Digital subtraction angiography
GDA	Gastroduodenal artery
HCC	Hepatocellular carcinoma
MVP	Micro vascular plug
PVA	Polyvinyl alcohol
SMA	Superior mesenteric artery
TACE	Transcatheter arterial chemoembolization
TAE	Transcatheter arterial embolization

S. W. Ryu (✉) · U. Pua
Department of Diagnostic Radiology,
Tan Tock Seng Hospital, Singapore, Singapore

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_21

1 Introduction

Bleeding can present as an acute, life-threatening medical emergency or as a chronic slow process with symptoms of anaemia. In the palliative setting, majority of the patients will have underlying advanced malignancy, with bleeding occurring in up to 10% of patients with advanced cancer (Niekamp et al. 2017). The cause of haemorrhage varies from local vessel damage and tumoural vascular invasion to systemic processes such as disseminated intravascular coagulopathy and thrombocytopaenia (Niekamp et al. 2017). Other subsets of palliative patients are those with end-stage medical conditions, whereby inflammation or infection may cause vessel injury and bleeding. More often these patients are not candidates for surgical management given their limited life-expectancy. Short-term benefit, however, may be achieved with endovascular embolization. Imaging diagnosis is often made with multiphasic computed tomography (CT), which can demonstrate high attenuation haemorrhage or active arterial extravasation and assists in identification and embolization planning of the bleeding artery (Fig. 1). This chapter will discuss techniques and embolic agents that can be used for bleeding in the hepatobiliary and pancreatic systems.

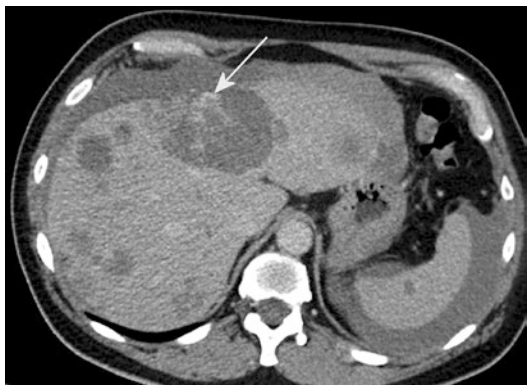


Fig. 1 Axial contrast-enhanced portal venous phase CT of a 73-year-old male with metastatic liver disease demonstrates active contrast extravasation (arrow) from a large segment 4 metastasis indicative of active bleeding. Also note multiple smaller liver metastases and high density haemoperitoneum

2 Indications

Patients with hepatobiliary and pancreatic bleeding can present with abdominal pain, haematemesis or signs of shock. Apart from traumatic causes, hepatocellular carcinoma (HCC) is the commonest cause of spontaneous haemorrhage worldwide (Srinivasa et al. 2015). The incidence of spontaneous rupture of HCC is 3–15% (Butt et al. 2016; Fan et al. 2018; Kim et al. 2012; Kirikoshi et al. 2009; Lai and Lau 2006; Tanaka et al. 2001; Yang et al. 2014; Zhu et al. 1996), with mortality rates ranging from 25 to 75% (Lai and Lau 2006; Yang et al. 2014). Haemorrhage secondary to metastases from sarcoma, gastrointestinal, renal and pulmonary carcinoma, melanoma and choriocarcinoma have also been reported (Srinivasa et al. 2015; Lok et al. 2005). Bleeding from a ruptured pancreatic neoplasm is much more rare (Tokue et al. 2017), with haemorrhage secondary to infection or inflammation being more common in the pancreatic region. In cases of HCC, bleeding is thought to result from venous congestion from tumour invasion with subsequent increase in pressure within the tumour. Bleed into such tumours further increase the pressure resulting in splitting of the liver capsule and rupture of the tumour (Kirikoshi et al. 2009; Zhu et al. 1996). Although surgical resection remains the curative treatment of choice for HCC, in most palliative patients, surgical management will not add any benefit to the overall survival with increased morbidity. The primary aim in managing a ruptured HCC is to achieve haemostasis (Kim et al. 2012). Transcatheter arterial embolization (TAE) has been reported to improve survival when compared to conservative therapy (Fan et al. 2018; Kirikoshi et al. 2009; Yang et al. 2014) with high success rates and lower mortality rates than surgical haemostasis (Lai and Lau 2006). Haemostasis with transcatheter arterial chemoembolization (TACE) for ruptured HCC have also been described with favourable results (Kim et al. 2012), however, may not be a feasible option in an acute emergency setting.

3 Contraindications

General contraindication to angiographic embolization is life-threatening anaphylaxis to iodinated contrast agent and unstable patient who requires urgent surgical management. In a bleeding patient, renal failure due to contrast load is generally of less concern. For hepatic embolizations, complete portal vein occlusion is thought to be a contraindication due to high risk of hepatic infarction (Lai and Lau 2006). Other relative contraindications include substantial arteriovenous or arterioportal shunting (Niekamp et al. 2017).

4 Anatomy

Thorough understanding of the arterial anatomy and its variants is required to safely perform endovascular embolization. Variant anatomy in the hepatic arteries have been well described with over 40% of the patients demonstrating a variant (Thacker et al. 2009). Common variants include replaced or accessory right hepatic artery from the superior mesenteric artery (SMA), replaced left hepatic artery from the left gastric artery and common hepatic artery arising from the SMA. In cases of peripheral hypervascular liver tumours, careful attention must be made to assess for parasitized extrahepatic feeding arteries, such as the inferior phrenic artery, especially if prior chemoembolization has been performed to the tumour.

The pancreatic head and duodenum is supplied by the pancreaticoduodenal arcade, which consists of superior and inferior, posterior and anterior pancreaticoduodenal arteries, branches of the gastroduodenal artery (GDA) and SMA, respectively. The GDA may arise from the right hepatic artery and from the coeliac axis (Loffroy et al. 2015). The arch of Buhler is a persistent embryonic anastomosis between the celiac artery and the proximal SMA, which is seen in 1% of the population. The dorsal, greater (arteria pancreatica magna) and transverse pancreatic arteries arising from the splenic artery supplies the body and tail of the pancreas.

5 Technique

5.1 Preparation

Any patients with suspected bleeding should be adequately assessed and resuscitated appropriately. Multiphase CT allows for confirmation of active bleeding. Anaesthetic support will likely be required in bleeding patients. Intravenous blood products such as packed red blood cells, platelets or fresh frozen plasma may be required, especially in patients with coagulopathy.

5.2 Access

Arterial access can be performed through the common femoral artery with insertion of a 5Fr/6Fr introducer sheath. Transradial access is also a safe alternative to the conventional transfemoral approach (Posham et al. 2016). More recently anatomic snuffbox distal radial artery access has been described for visceral intervention (Pua et al. 2018) (Fig. 2). Transradial or

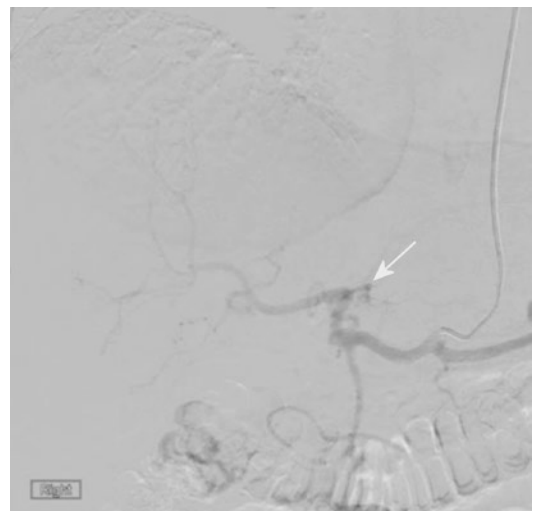


Fig. 2 Coeliac angiogram demonstrates segmental artery to the liver metastasis (arrow) without evidence of active bleeding. Right snuffbox radial approach was used with a 5Fr Glide Sheath Slender (Terumo, Tokyo, Japan) and a 5Fr 110 cm Jacky (Terumo) angiographic catheter

snuffbox radial access requires a minimum artery diameter of 1.6 mm for 5Fr and 2.0 mm for 6Fr Glide Sheath Slender introducer sheaths (Terumo, Tokyo, Japan). Although transradial access has advantages of early mobilization, low incidence of severe bleeding complications and ease of haemostasis (Pua et al. 2018), it may not be a feasible option in patients who are in hypovolaemic shock with reduced vessel calibre and presence of radial arterial lines.

5.3 Catheter Choice and Angiography

Cannulation of the coeliac artery from femoral access can be made using reverse-curve 5Fr catheters (Sheperd Hook, Simmons 1). The SMA can be cannulated using a 5Fr Cobra catheter. In cases of replaced right hepatic artery from the SMA, a 5Fr RH catheter can be used, in which the right facing tip accommodates the origin of the right hepatic artery. Longer catheters such as 110 cm Jacky/Sarah or 100 cm Cobra are required to reach the coeliac artery and SMA with the transradial approach. An abdominal aortogram with a 5Fr pigtail catheter may be required in patients with hepatocellular carcinomas in order to identify parasitized feeding vessels.

These angiographic catheters are used to engage the coeliac and superior mesenteric arteries whereby power injection digital subtraction angiography (DSA) can be performed at rates of 4–5 mL/s with 16–20 mLs of contrast. Extravascular contrast extravasation is indicative of active bleeding. It is not uncommon to be faced with a negative DSA, especially after vigorous resuscitation and reversal of coagulopathy. In such cases, careful evaluation should be done to assess for truncated or irregular vessels, aneurysms and arteriovenous or arterioportal fistulas, which are most likely to be the source of the bleed (Fig. 3). Various microcatheters are available which can be used coaxially for selective angiogram and embolization.

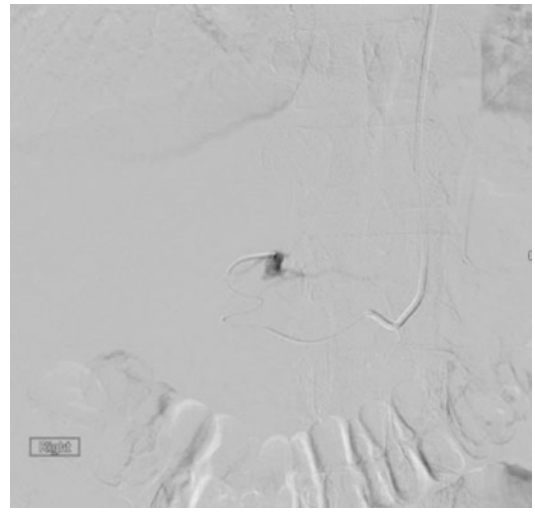


Fig. 3 SMA angiogram in a 78-year-old female who presented with retroperitoneal haematoma shows a pseudoaneurysm arising from the inferior pancreaticoduodenal artery. Right common femoral artery access was used and the SMA was selected using a 5Fr Cobra catheter

5.4 Embolic Agents

The type of embolic agent is dependent on number of factors, including vascular anatomy, angiographic findings, coagulation state, achievable catheter position and the operator preference (Shin 2012).

5.4.1 Coils

Coils are permanent embolic agents made of stainless steel or platinum that act by causing mechanical obstruction and inducing thrombosis (Leyon et al. 2014; Madhusudhan et al. 2016), and thus intact coagulation profile is required. Various diameter, lengths and shapes of coils are available that can be delivered through angiographic or microcatheter systems. Fibred coils increase thrombogenicity (Madhusudhan et al. 2016). Coils are also classified as detachable or non-detachable coils. Detachable coils have the advantage of retrievability and redeployability, but come with increased cost (Figs. 4 and 5). Non-detachable coils can be deployed using a pusher wire or with saline flushes. In order to

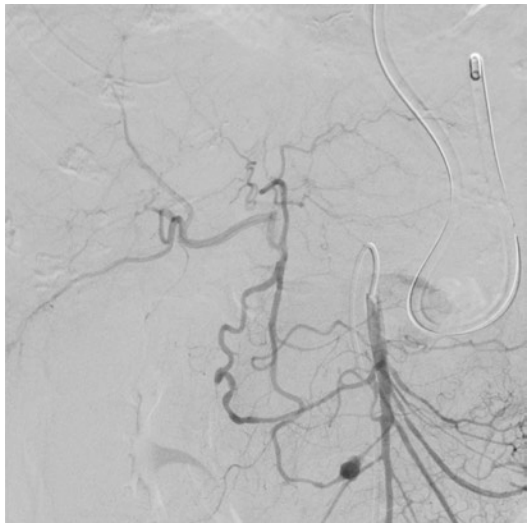


Fig. 4 A 2.4Fr Progreat microcatheter (Terumo) was used coaxially to perform coil embolization distal and proximal to the aneurysm

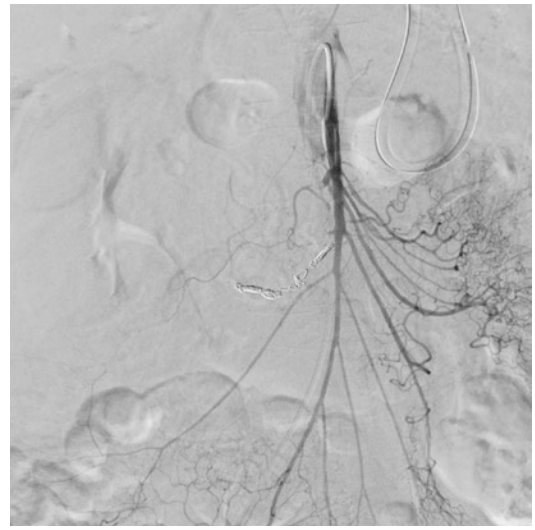


Fig. 6 Right gastric artery angiogram after coil embolization in a patient being worked up for Y90 radioembolization demonstrates persistent flow

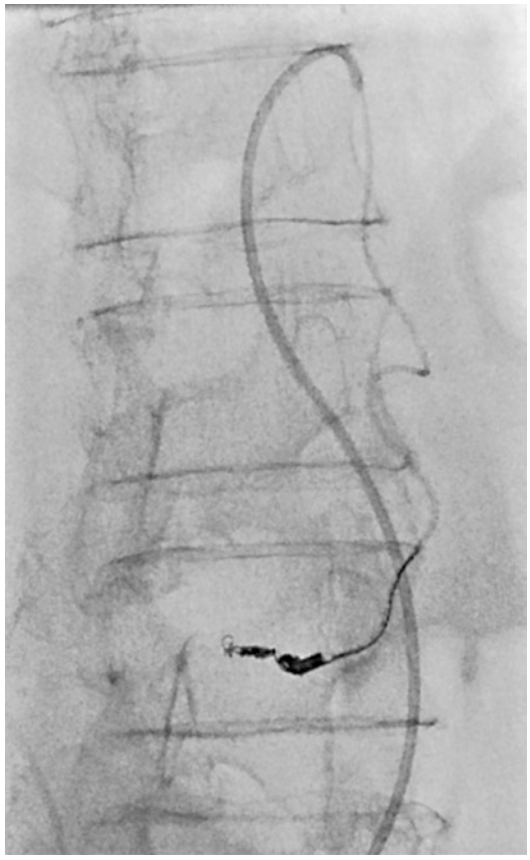


Fig. 5 Completion SMA angiogram demonstrates successful embolization of both 'front' and 'back' door arteries

avoid non-target embolization coils must be deployed at the desired site; thus achieving catheter position is important. The diameter of the selected coils should be 20–30% larger than that of the intended vessel. Undersizing coils runs the risk of distal migration or inadequate embolization (Fig. 6) and oversizing will not allow formation of the intended configuration (Leyon et al. 2014). Coils can also be used with other embolic agents; for instance, in cases of arteriovenous or arterioportal shunts associated with bleeding HCC, coils may be used first to shut down the shunt, followed by embolization with gelfoam particles (Fan et al. 2018).

5.4.2 Particulate Embolic Agents

Gelfoam (Pfizer, NY) is a water-soluble temporary embolic agent derived from pork skin gelatin. Once delivered, it forms a surface of thrombogenesis. Gelfoam can be formed as slurry when mixed with contrast, to allow fluoroscopic visualization during delivery. The Gelfoam particles become smaller with more vigorous mixing, thus allowing for more distal embolization. Gelfoam can also be cut into small pellets and delivered via a syringe flush (Fig. 7). Most vessels are thought to recanalize in 3 weeks to 3 months after Gelfoam embolization (Leyon

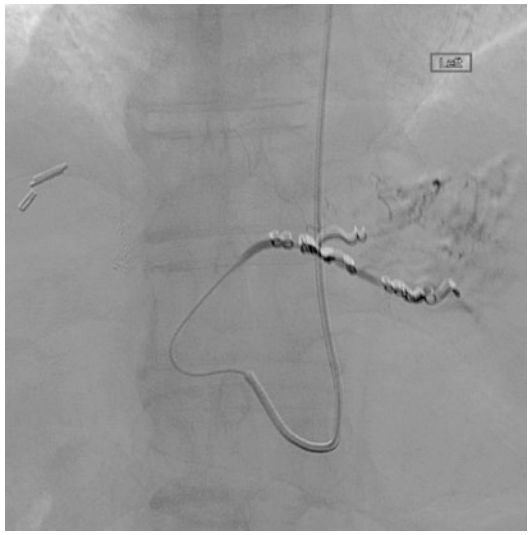


Fig. 7 Selective angiogram from a 2.4Fr 130 cm Progreat microcatheter (Terumo) in the segmental artery after gelfoam slurry embolization demonstrates pruning of the artery

et al. 2014). For bleeding HCC, Gelfoam is the preferred embolic agent as opposed to permanent particles or coils (Srinivasa et al. 2015; Lai and Lau 2006). The temporary nature of Gelfoam allows recanalization of the embolized artery for future TACE.

Polyvinyl alcohol (PVA) and microspheres are permanent embolic agents that are manufactured in various sizes ranging from 40 to 1200 μm, with smaller particles capable of achieving more distal embolization. The particles adhere to the vessel wall, thus slowing flow and inducing thrombosis (Leyon et al. 2014). For upper gastrointestinal tract embolization, typically 300–500 μm sized particles are used. These are mixed with 10 or 20 mLs of contrast to allow fluoroscopic visualization during delivery.

5.4.3 Liquid Embolic Agents

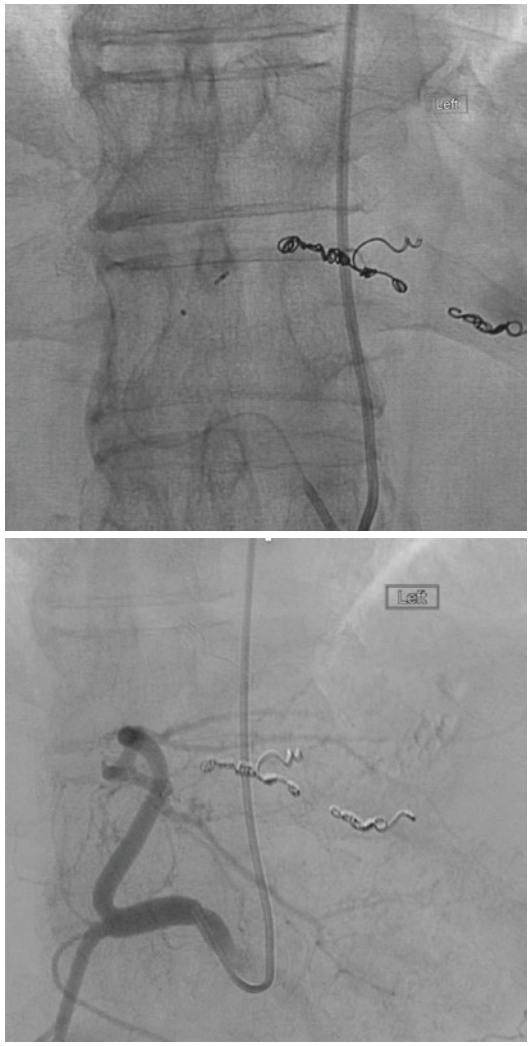
Glue (*N*-butyl cyanoacrylate) is a permanent liquid embolic agent that rapidly solidifies on contact with ionic solutions such as blood or saline (Leyon et al. 2014). Glue is an effective embolic agent in patients with coagulopathy unlike coils and also allows embolization of sites where microcatheter position is not achievable, including embolization of collateral feeding vessels. All equipment used must be flushed with non-ionic 5% dextrose solution to prevent unwanted polymerization. Glue is mixed with lipiodol, an oil emulsion that acts as a carrier and is also radiopaque. Different glue-lipiodol mixture ratios can be used depending on the desired rate of polymerization. Glue has been successfully used in haemorrhagic liver lesions and upper gastrointestinal bleeding (Hur et al. 2017; Monsignore et al. 2012).

5.4.4 Vascular Plugs

Amplatzer vascular plugs (AVP) (St. Jude Medical) are cylindrically shaped self-expanding nitinol wire mesh which are deployed by unsheathing and unscrewing (Madhusudhan et al. 2016; Ramakrishnan 2015). This allows repositioning of the plug possible prior to deployment. There are four types of AVP (I, II, III and IV) with different sizes and designs. The choice of AVP depends on the size of the vessel, flow dynamics and the available landing zone (Madhusudhan et al. 2016). All AVP devices must be oversized by 30–50% of the native vessel. Its mechanism of action is similar to coils, causing mechanical obstruction and promoting thrombosis and is intended for use in medium to large sized vessels as they are delivered through 4–7Fr guiding sheaths or 5–9Fr guiding catheters. AVP IV is the only type that can be delivered through a 5Fr catheter that accommodates a 0.038 inch guidewire. Therefore, the use of AVP in hepatobiliary bleeding is limited to vessels such as the GDA (Abdel-Aal et al. 2011). Newer micro vascular plugs (MVP) (Medtronic) are available in 3 and 5 mm sizes that are delivered through a microcatheter system allowing superselective embolization (Figs. 8 and 9), but there is limited data for its use in setting of hepatobiliary haemorrhage.

5.5 Embolization Techniques

The aim of embolization is to achieve stasis in the bleeding artery. When possible, superselective catheterization of the bleeding artery is performed. This reduces the risk of potential



Figs. 8 and 9 A MVP-5Q (Medtronic) was deployed in the right gastric artery with immediate cessation of arterial flow. The MVP can only be seen as two dot markers. With correct sizing and appropriate landing zone, vascular plugs provide excellent embolization results

non-target embolization. In cases of bleeding from the GDA where there is collateral arterial inflow, back pressure may allow continued bleeding if embolization is only performed proximally (Shin 2012). In such cases both 'front' and 'back' door arteries are embolized, also known as the sandwich technique. Completion angiogram from both coeliac artery and SMA must be performed to ensure no collateral supply persists.

6 Complications

Complications can be classified to general, access site related and procedure specific. General complications include potential contrast allergy, contrast induced nephropathy and infection. Access related complications include haematoma, bleeding, dissection and pseudoaneurysm formation. With regard to the embolization procedure, non-target embolization is an important complication to be aware of and avoided. This is more of an issue when using agents such as Gelfoam slurry, PVA particles and particularly glue, where understanding of the blood flow velocity and flow dynamics are crucial to avoid reflux and unwanted embolization. PVA particles may also be clumped within the microcatheter and glue can also cause catheter trapping and fragmentation.

7 Conclusion

Transcatheter arterial embolization for haemorrhage in the hepatobiliary and pancreatic system is a safe procedure associated with low morbidity and high success rates. It is particularly useful in palliative patients whereby targeted minimally invasive treatments can be offered, improving the quality of the remaining life. Currently, various embolic agents are available for the interventionalist to use, and will differ for each patient based on the clinical picture and vascular anatomy.

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Bleeding Solutions for Fungating Masses

Karthikeyan Damodharan,
Nanda Venkatanarasimha, Kristen Alexa Lee,
and Sivanathan Chandramohan

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Abstract

Fungating masses are common in advanced cancers, which are marked by skin involvement and necrosis. They can present with life-threatening haemorrhage. Management of bleeding in this palliative patient cohort is complex and requires a multidisciplinary approach. Interventional radiology has an established role in the management of bleeding from malignant tumours and can be effectively used to treat bleeding from such masses.

K. Damodharan · N. Venkatanarasimha · K. A. Lee
S. Chandramohan (✉)
Department of Vascular and Interventional Radiology, Singapore General Hospital, Singapore, Singapore
e-mail: sivanathan.chandramohan@singhealth.com.sg

1 Introduction

Fungating mass generally refers to a malignant mass that resembles a fungus in its appearance due to their rapid outward growth. They are characterised by ulcerations involving the skin or the surface of the involved organ, which can present with bleeding.

The earlier chapters in this section describe in detail the management of bleeding from various internal organ systems due to malignant masses.

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_22

Hence in this chapter, we will focus on the solutions for bleeding specifically from fungating masses, which involve the skin. Such lesions are referred to as malignant fungating wounds (MFW).

MFWs usually appear in patients with advanced cancer in the late stage and the treatment is usually palliative. The average life expectancy of this group of patients is usually 6–12 months (Grocott et al. 2013).

2 Etiology

Fungating masses can be either a primary or metastatic tumour that invades the epithelium and the adjacent lymphatics and blood vessels (Bergstrom 2011). These lesions occur in 5% of patients with primary tumour and 10% of patients with metastases (Grocott et al. 2013).

Fungating masses can arise from any type of malignancy, but are commonly seen with cancers of the breast, head and neck, kidney, lung, ovary, colon, skin, bladder, penis, sarcoma leukaemia, and lymphoma (O'Brien 2012). Breast cancer tops the list (49%) of fungating mass (Probst et al. 2009).

Fungating masses often present with bleeding due to the following reasons:

1. tumour eroding the capillaries/major blood vessels
2. minor trauma during removal of the dressing adherent to the wound surface
3. coagulation disorders related to the systemic disease (Woo and Sibbald 2010)

3 Clinical Presentation

Fungating masses present with one of the following symptoms: pain, discharge, odour, bleeding, pressure symptoms due to mass effect such as airway obstruction and psychological stress. Infection of the fungating masses results in offensive odour, excessive amounts of exudative discharge, frequent bleeding, and cause psychosocial distress to the patients (Recka et al. 2012).

4 Management of Bleeding from Fungating Masses

Bleeding from fungating lesions can be challenging for the patient, caregivers as well as the palliative care team. The treatment often requires a multidisciplinary team effort and a holistic approach. The primary intent of the treatment in these patients with advanced disease is the preservation of the quality of life and comfort care. In terminally ill patients where the goal of care is comfort, invasive treatments may be burdensome rather than beneficial (Guenette et al. 2017).

The management of bleeding fungating wound involves local wound care, treatment of associated systemic symptoms such as pain, anxiety or hypovolaemia, and definitive measures to arrest the bleeding.

4.1 Local Wound Care

Proper local wound care can reduce the incidence of bleeding.

Gentle application and removal of dressing, applying non-adherent contact layer dressing, moistening the dressing pre-removal if adherent and avoiding unnecessary debridement and dressing changes are some of the measures to minimise the risk of bleeding (Recka et al. 2012). Patient and caregivers should be educated to apply steady pressure with dark linen, in case of bleeding while at home or hospice (Harris and Noble 2009).

Mild to moderate bleeding can be managed with gentle compression with an ice pack or haemostatic agents such as calcium alginate for 10–15 min. Local application of silver nitrate sticks at the bleeding points may also be used (Recka et al. 2012).

Woo et al. describes in detail the various topical haemostatic/vasoconstrictor/cauterising agents that can be applied in cases of persistent bleeding as well as oral agents that can be used (Woo and Sibbald 2010).

4.2 Systemic Treatment

Bleeding can trigger anxiety/emotional distress to the patient. Opiods and benzodiazepines can be used to treat the patient's anxiety as well as any associated pain (Harris and Noble 2009).

In patients with severe persistent bleeding, resuscitation with intravenous fluids and blood products are usually required. Such patients require care at an acute hospital setting, depending on the specific goals of treatment.

Bleeding may be due to coagulopathy from bone marrow suppression or disseminated intravascular coagulation, which requires appropriate correction.

Antifibrinolytic agents such as aminocaproic acid, tranexamic acid can be given via oral or intravenous routes to control bleeding.

4.3 Interventional Radiology

Interventional radiology (IR) has an increasing role in the management of those patients with persistent severe active bleeding. IR therapy is more suited for definitive management of bleeding in these patients with advanced disease due to the minimally invasive nature of the procedures. Majority of the treatment can be performed under local anaesthesia/moderate conscious sedation with good success and minimal complication rates.

4.3.1 Embolisation

As early as 1978, Harrington et al. reported transcatheter embolisation in the successful management of bleeding from fungating mass from locally advanced breast cancer (LABC). Similarly, there have been several reports of haemorrhage from fungating masses of the breast, head, and neck treated successfully with embolisation. Hence, it would be beneficial for the primary team to involve the IR early on in these patients with severe life-threatening bleeding.

In haemodynamically stable patients, a CT angiogram of the region involved would be useful for planning definitive IR intervention. The CT helps to identify/localise the bleeding vessel with high sensitivity and specificity, as well as delineate the vascular supply to the tumour mass. Especially, in head and neck masses the blood supply can be from common carotid or internal carotid which can pose challenges to embolisation. CT angiogram mapping will help to identify this potential trap and potentially reduce the procedure time, iodinated contrast volume, and radiation dose to the patient.

Ideally, the interventional radiologist should have a discussion with the patient and/or the caregivers about the proposed treatment plan, potential risks, and expected outcome of the treatment. This would help to allay the anxiety of the patient and the caregivers and manage their expectations of the procedure in such stressful situations.

The procedure is best performed in a dedicated interventional angiography suite with cone beam CT facility and the necessary equipment for embolisation readily available such as diagnostic catheters and embolic materials. Most procedures can be performed with local anaesthesia or moderate conscious sedation, obviating the need for general anaesthesia and their inherent risks in these unstable patients. In oropharyngeal or lung tumours with the risk of aspiration due to bleeding in to the airway, intubation is required to protect the airway.

Digital subtraction angiography is performed to localise the bleeding vessel/abnormal vessels supplying the tumour. Selective catheterisation using standard catheters and super selective catheterisation with micro catheters may be required to prevent non-target embolisation.

Angiographic findings include active contrast extravasation, pseudo aneurysm, vessel irregularity, or abnormal tumour blush.

Embolisation can be performed using permanent embolic materials such as particles, liquid embolics (such as histoacryl glue or coils), or temporary embolic agents such as gel foams and

autologous blood clot. The author prefers permanent embolic agents such as particles to provide irreversible distal vessel occlusion.

Embolisation in general is very successful in achieving cessation of bleeding. The potential risks of the procedure include access site bleeding/pseudo aneurysm, non-target embolisation, vessel injury, infection, post-embolisation syndrome.

Rzewnicki et al. reported a success rate of 86% in patients who underwent emergent embolisation for bleeding fungating masses of the head and neck in 76 patients. The most frequent complications were minor (headache in up to 18% of patients). One patient developed haemiparesis (1.3%) post-embolisation.

These patients may be potentially treated with radiotherapy or de-bulking surgery to minimise the risk of future bleeds after the embolisation.

The potential advantages of embolisation include possibility of occluding surgically inaccessible arteries (especially in extensive head and neck tumours), shorter procedure time, avoid risks of general anaesthesia in these unstable sick patients, lower complication rates compared to surgery, reduced the risk of damage to adjacent healthy tissue and facilitate subsequent surgery/radiotherapy (Rzewnicki et al. 2012).

4.3.2 Stent Graft Insertion

In some cases, the bleeding is due to tumour eroding a large artery such as the axillary artery, which cannot be embolised as it provides significant supply to other normal tissues. This can be successfully treated by stent graft placement across the abnormal segment as described by Ugras et al. in 2015.

4.3.3 Transarterial Chemo Embolisation (TACE)

TACE and intra-arterial chemo infusion in patients with locally advanced breast tumours have been reported to be safe and effective (Morimoto et al. 1985; Zhang et al. 2013). Zhang et al. showed that 85.7% of patients had partial or complete response. This approach reduces tumour volume, decreases extent of infiltration of skin and muscle, and increases surgical resection rate (Zhang et al. 2013).

4.3.4 Image-Guided Tumour Ablation

Van Sonnenberg et al. reported radiofrequency ablation (RFA) of bleeding inoperable locally advanced breast cancer to achieve successful symptomatic relief (2005). Similarly, RFA has shown to be effective for palliation in advanced head and neck tumours unsuitable for surgery/radio or chemotherapy (Owen et al. 2011).

Cryoablation has also been shown to be effective in advanced breast and head and neck tumours with very low complication rates (Littrup et al. 2009; Guenette et al. 2017).

Chemo embolisation/chemo infusion and ablation therapies are not ideal in patients with active bleeding from fungating masses. They can reduce tumour size and rate of progression and thereby potentially reduce their risk of future bleeding. Hence, they can be useful in treating patients with large fungating masses to prevent the risk of significant bleed.

4.4 Surgery

Surgical resection of the bleeding tumour or ligation of a larger vessel supplying the involved region may be performed. But only a minority of these patients with advanced cancer may be ideal candidates for major surgery or even general anaesthesia (Pereira 2004). Salvage surgery for advanced tumour carries higher complication rates (Guenette et al. 2017). As mentioned earlier, the patients may be suitable for de-bulking surgery post-embolisation to prevent future bleeds.

4.5 Radiation

External beam radiotherapy can reduce the size of the fungating wound and control the symptoms of bleeding, pain, and exudate (Alvarez et al. 2007).

5 Conclusion

Bleeding from fungating malignant masses can be caused by various cancers and can range from chronic low volume bleed to acute life-threatening haemorrhage. They can be treated with various modalities including local topical agents, systemic therapies, and interventional radiology. The treatment needs to be tailored with an overview of the goals of care specific to the patient.

Interventional radiology plays an increasing role in the prevention and management of this condition. It is important for interventional radiologists to ensure that the oncologists and palliative care physicians are aware of the interventional radiology solutions available.

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Part VI

Obstruction Solutions

Malignant Bile Duct Obstruction (MBDO): Obstruction Solutions for Liver and Gallbladder

Kheng Song Leow and Rahul Lohan

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K. S. Leow (✉) · R. Lohan
Department of Diagnostic Radiology, Woodlands Health Campus, Singapore, Republic of Singapore

Department of Diagnostic Radiology, Khoo Teck Puat Hospital, Yishun Central, Singapore, Republic of Singapore
e-mail: leow_kheng_song@whc.sg; lohan.rahul@ktph.com.sg

Abstract

Biliary obstruction secondary to malignant causes has a dramatic effect on the quality of life of the patients with already shortened life expectancy. At the time of diagnosis, these

© Springer Nature Switzerland AG 2021

P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_23

patients are usually in the advanced stage of disease. VIR has an important role in relieving malignant bile duct obstruction (MBDO). Planning is essential to achieve the goal of optimal drainage with the least number of drains or stents. Gentle handling can minimize procedure-related complications.

Abbreviations

CT	Computed tomography
ERCP	Endoscopic retrograde cholangiopancreatography
MBDO	Malignant bile duct obstruction
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
PTBD	Percutaneous transhepatic biliary drainage
PTC	Percutaneous transhepatic cholangiography

1 Introduction

Obstruction of the biliary system from malignant causes dramatically affect the quality of life in the patients with already shortened life expectancy. The common malignant causes include malignancies arising from the pancreaticobiliary system (e.g. cholangiocarcinoma, gallbladder carcinoma and pancreatic carcinoma), liver (e.g. hepatocellular carcinoma and metastases) and compressive hilar lymphadenopathy (from lymphoma or nodal metastases). By the time the diagnosis is made, the patients are usually in the advanced stage of disease and methods to relieve the biliary obstruction become essential element of the palliative care (Brown and Covey 2008).

Malignant biliary duct obstruction (MBDO) manifests as painless jaundice, elevated serum bilirubin (conjugated hyperbilirubinemia, due to impaired excretion), dark-coloured urine (bilirubinuria) and light-coloured acholic stool. The most debilitating symptom perhaps being the skin pruritus. The exactly pathophysiology is still not well understood, but it was believed to be attributed to retention of bile salts secondary to biliary obstruction. Patients who have suffered from this presentation tend to have a poorer quality of life. Infrequently, patients with previous interventions (e.g. endoscopic retrograde cholangiopancreatography, ERCP or sphincterotomy) or surgery (e.g. bilio-enteric bypass) can first present with cholangitis, manifested as Charcot triad, evidenced by fever, right hypochondrium pain and jaundice (Sutter and Ryu 2015).

Relieving obstruction via drainage or stent placement in patients with MBDO often leads to considerable clinical and biochemical improvement. Sometimes without drainage, they are precluded from chemotherapy for fear of toxicity, as the drugs are metabolized and excreted by the liver. If remains untreated, MBDO can lead to liver failure (Ballinger et al. 1994).

Endoscopic retrograde cholangiopancreatography (ERCP) and biliary drainage (ERBD) are preferred method of relieving biliary obstruction involving the common bile duct or common hepatic duct sparing the biliary confluence. Bile duct obstruction proximal to the confluence of right and left hepatic ducts is often managed by percutaneous interventional radiological procedures, as are the patients in whom ERBD is not technically feasible or has failed (Brown and Covey 2008). The various percutaneous biliary interventions used in the management of MBDO include percutaneous transhepatic cholangiography (PTC), endobiliary biopsy, percutaneous transhepatic biliary drainage (PTBD) and stent placement (Krokidis and Hatzidakis 2014).

2 Indications

Palliative biliary drainage improves liver function, resolves jaundice and reduces the risk of sepsis. Increased bilirubin levels eventually result in encephalopathy and multiorgan failure. The lack of bile flow towards the intestine predisposes to increased bowel wall permeability, portal system bacteraemia and systemic sepsis. Improved liver function from drainage allows initiation of palliative chemotherapy. The patients of MBDO

Table 1 Indications for percutaneous transhepatic biliary drainage

1.	Relief of biliary obstruction
2.	Relief of obstructed and infected biliary system (e.g. cholangitis)
3.	Allow initiation of chemotherapy
4.	Diversion of bile leak to allow healing

presenting with cholangitis and septicaemia would require percutaneous drainage for source control on top of aggressive intravenous antibiotics. Less commonly, percutaneous biliary drainage can help to divert bile drainage to allow healing in post-operative patients who suffer from bile leak (Sutter and Ryu 2015) (Table 1).

3 Contraindications

Uncorrected coagulopathy is an absolute contraindication, for fear of uncontrolled bleeding and mortality. Every effort should be made to correct the coagulation profile; however, these procedures may still be indicated if they have lower expected morbidity than alternative methods of diagnosis or treatment. Large ascites may complicate transhepatic biliary access and predispose to pericatheter leak. If left-sided access is not an option, paracentesis should be considered. Infection (e.g. cholangitis) requires PTBD, but stent placement is not advisable in septic patients. It is advisable to minimize manipulation in the infected and obstructed biliary system to reduce the chance of intravasation of bacteria and intraprocedural septic shock (Brown and Covey 2008).

4 Patient Preparation

Adequate pre-procedure preparation is the key to minimize complications and increase the success rate of the procedure. One of the pre-procedure preparations that cannot be over-emphasized is the administration of broad spectrum prophylactic antibiotics. The common choices are intravenous ceftriaxone, ampicillin/sulbactam, ampicillin and gentamicin. In patients allergic to penicillin, fluoroquinolone, vancomycin, clindamycin or an aminoglycoside should be administered (Krokidis and Hatzidakis 2014).

If there is coagulopathy, not uncommon in ill patients, it should first be corrected. Patients should have a platelet count of at least >50,000/dL and international normalized ratio (INR) of <1.5 before percutaneous puncture is performed. Percutaneous biliary procedures are painful. Moderate sedation (using intravenous Midazolam +/− Fentanyl) is necessary for almost all cases. Complex prolonged biliary procedures may warrant general anaesthesia. Thus, only clear fluids are allowed for 4 h before the procedure. The patients should have good intravenous (IV) access for administration of hydration, sedative agents and antibiotics. Hydration (early goal-directed therapy) is critical in patients who are at risk of septic shock from cholangitis (Krokidis and Hatzidakis 2014).

5 Relevant Anatomy and Variants of Biliary Tree

5.1 Relevant Anatomy

There are three important structures in the biliary tree which affect the disease prognosis and percutaneous intervention. The first structure is the cystic duct that in normal anatomy, should join the common hepatic duct (CHD) to form the common bile duct (CBD). This structure divides the biliary system into "*high*" (above the cystic duct insertion) and "*low*" (at and below the insertion of cystic duct) levels, commonly used to describe the level of obstruction in MBDO (Sutter and Ryu 2015).

The second important landmark is the biliary hilum, aka the *primary* confluence of the right and left main hepatic ducts. Besides its surgical importance, as illustrated in *Bismuth and Corlette* classification of cholangiocarcinoma (Fig. 1), it divides the biliary tree into intrahepatic and extrahepatic bile ducts (Brown and Covey 2008).

The third important landmark is the confluence of segment 2 and segment 3 bile ducts (on the left side) and confluence of right anterior and right posterior sectoral ducts (on the right side).

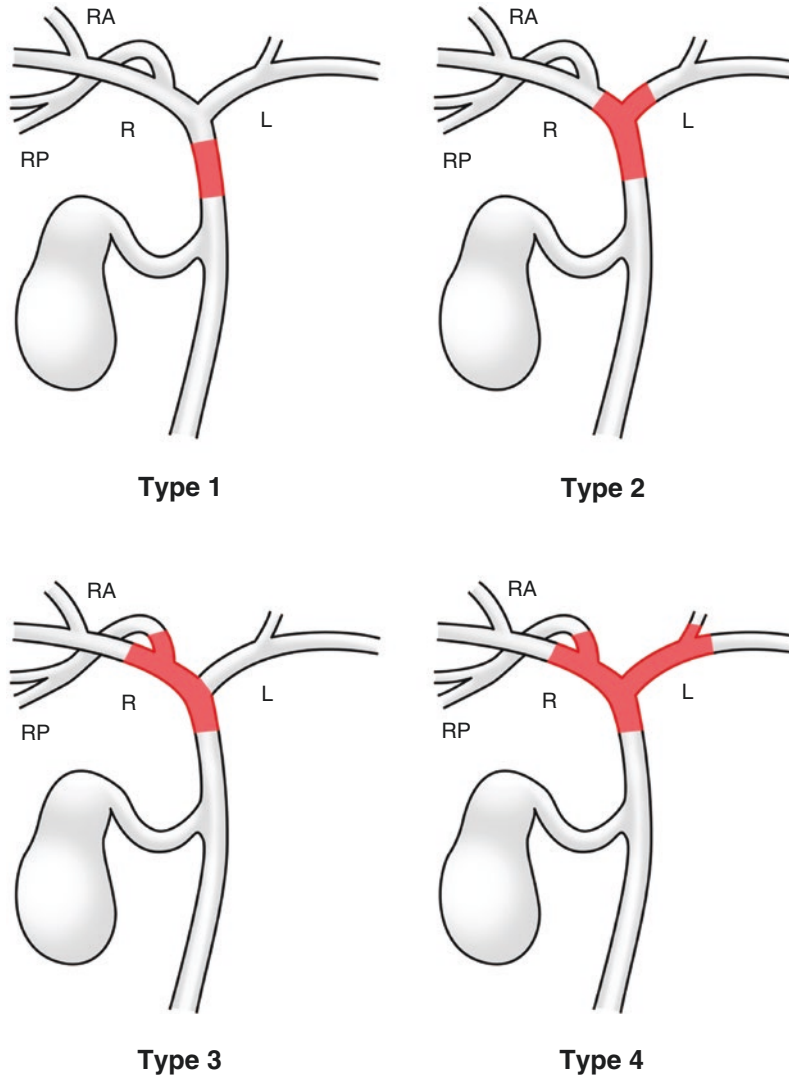

Fig. 1 Bismuth and Corlette classification. Type 1: Tumour in the CHD (hilum/primary confluence is spared). Type 2: Tumour obstructs the hilum (aka primary confluence). Type 3: Tumour involves the unilateral (right *or* left) secondary confluence. Type 4: Tumour involves the bilateral (right *and* left) secondary confluences

Also known as *secondary* confluence; it is used in Bismuth classification (Brown and Covey 2008) of the MBDO.

5.2 Relevant Variants of Bile Ducts

There are several common biliary ductal anatomical variants (Fig. 2). They occur in up to 20% of patients. They include trifurcation of hepatic ducts (type II), right posterior hepatic duct draining into the left hepatic duct (type IIIA), right posterior hepatic duct draining into common hepatic duct (type IIIB) and right posterior hepatic duct draining into cystic duct (type IV). Recognition of these variants is important, as the percutaneous drainage approach can be completely different if one of these variants is present.

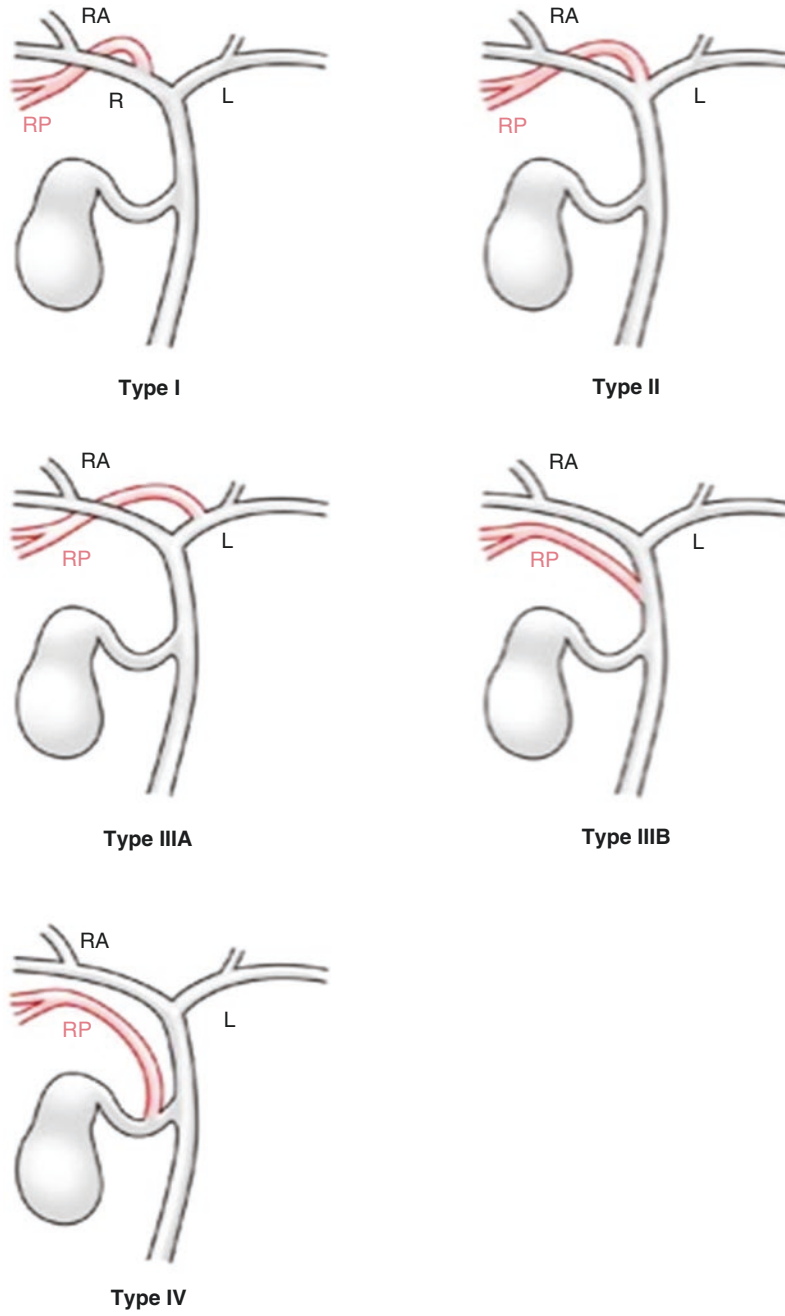

Fig. 2 Variant of biliary tree. *Type I:* typical normal biliary anatomy. *Type II*: trifurcation of sectoral ducts. *Type IIIA*: right posterior sectoral duct draining into left sectoral duct. *Type IIIB*: right posterior sectoral duct draining into CHD. *Type IV*: right posterior sectoral duct draining into cystic duct

6 Evaluation of Imaging Pertinent to Technique

Ultrasonography (US), though is easily accessible, is often inadequate, especially when bowel gas obscures the visualization of mid to distal CBD. It does come in handy as the first-line imaging modality to exclude gallstone or acute cholecystitis, but its role in management of MBDO is inadequate for both diagnosis and treatment planning (Brown and Covey 2008).

Table 2 Essential information in planning for PTBD/stent placement

(a)	Level of obstruction (high or low)
(b)	Bismuth classification and presence of isolation
(c)	Anatomical variants of bile ducts (e.g. right posterior sectoral duct draining into left hepatic duct)
(e)	Adequate functional liver parenchyma
(d)	Presence or absence of portal vein thrombosis

Cross-sectional imaging with computed tomography (CT) of the abdomen or magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) with intravenous contrast administration is required to confirm the presence of biliary obstruction and underlying malignant aetiologies. These modalities also provide excellent multiplanar three-dimensional (3D) information of the biliary anatomy, essential for planning of percutaneous biliary drainage or stent placement (Brown and Covey 2008).

The imaging information should be gathered, in a systematic manner (Table 2) with a goal to achieve optimal biliary drainage with as few drains or stents as possible.

6.1 Determining the Level of Obstruction

Low MBDO is defined by obstruction below the insertion of cystic duct to the CBD. The preferred method of treatment for this level of obstruction is via endoscopic approach (i.e. ERCP), with the aim to leave no external drain, if possible.

High MBDO is defined as bile duct obstruction at and above the insertion of cystic duct. In high MBDO, the preferred method of drainage is by percutaneous route, as endoscopic approach is rather challenging with higher failure rate.

6.2 Bismuth Classification and Presence of Isolation

The *Bismuth and Corlette* classification well established in surgical management of patients with cholangiocarcinoma can be extrapolated to percutaneous biliary interventions, when selecting patient and planning optimal drainage (Brown and Covey 2008).

Isolation occurs when the obstruction involves the central biliary hilum and extends along the central ducts, resulting in the absence of communication between segmental ducts. An example is illustrated in Fig. 3. Recognizing isolation is critical as adequate drainage of multiple segments may require multiple drains or stents (Sutter and Ryu 2015). There is no single best approach to various types of MBDO. A general guide is presented in Table 3 (Brown and Covey 2008; Sutter and Ryu 2015).

6.3 Anatomical Variants of Bile Ducts

On preprocedural imaging, the dilated bile ducts should be followed from liver segments centrally using an orderly search pattern to determine which ducts communicate and which ducts are isolated from each other. The variant anatomy can be encountered in up to 20% of cases. A common variant is the insertion of right posterior sectoral duct (segments 6 and 7) into the left hepatic duct instead of the right anterior sectoral duct. Pre-procedural identification of this variant in the setting of a hilar obstruction would persuade the operator for a single left PTBD, which would effectively drain six liver segments (segments 1 to 4, 6 and 7). A right PTBD placed into the right anterior sectoral duct (segments 5 and 8) may only drain two segments in such cases (Brown and Covey 2008).

6.4 Adequate Functional Liver Parenchyma

It is vital to estimate the fraction of functional liver to be drained. At least 30% of *functional* liver drainage is required for the elevated serum bilirubin to return to normal or near normal level. Higher percentage would be required if the

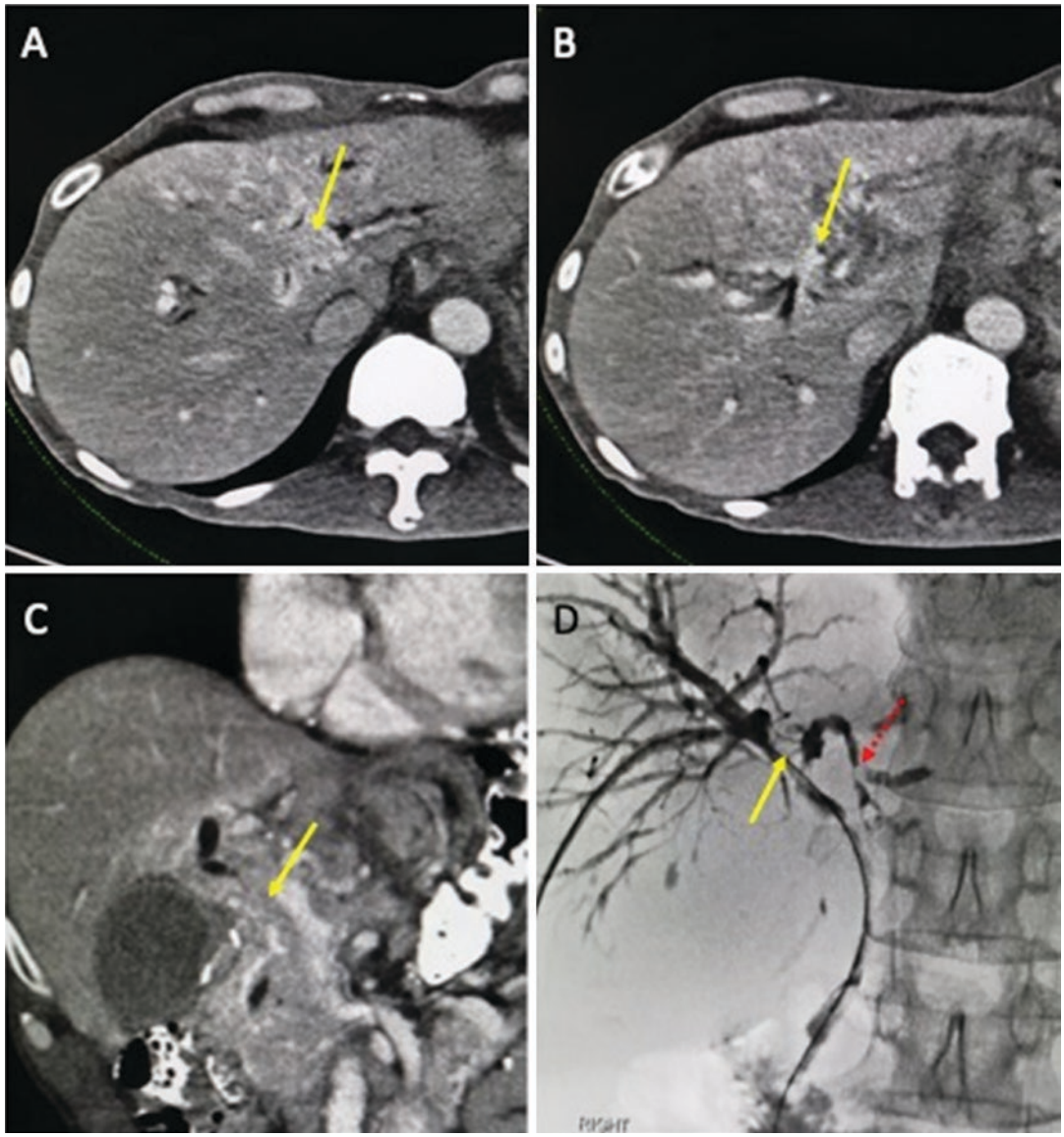

Fig. 3 Malignant hilar obstruction. (**a**, **b**) Contrast-enhanced axial CT images demonstrate enhancing tissue infiltrating the central hepatic ducts involving the secondary confluence on left (arrow, **a**) and right (arrow, **b**), suspicious for cholangiocarcinoma. (**c**) Infiltrative disease is also noted along the common bile duct (arrow). (**d**) Cholangiogram obtained via a right-sided percutaneous biliary drain shows irregular narrowing along the common bile duct, at the hilum (solid arrow) and confluence of segment ducts on left (red dotted arrow)

Table 3 General guide to planning PTBD/percutaneous biliary stenting

Bismuth type 1	1 drain or 1 stent (it is generally adequate)
Bismuth type 2	2 drains or 2 stents to drain each obstructed systems – T configuration – Y configuration
Bismuth type 3/4	3 drains or 3 stents (It is challenging, as the benefits of palliation decrease relative to the risks, but still technically viable)

underlying liver is dysfunctional. Draining an *atrophic* liver lobe is technically difficult, and will not improve the liver function. It would be equally ineffective to drain a segment of liver that is almost *entirely occupied* by tumour (Sutter and Ryu 2015).

6.5 Presence or absence of Portal Vein Thrombosis (PVT)

Identification of portal vein thrombosis (PVT) is equally important. In MBDO, PVT can lead to atrophy of a part or segment of liver. As normal liver parenchyma derives up to 80% of its blood supply from the portal vein, recovery of liver function depends upon the status of portal circulation. If the goal of palliation is to improve liver function, only liver segments with patent portal venous supply should be targeted during biliary drainage (Brown and Covey 2008).

7 Equipment

Equipment required for procedure of percutaneous transhepatic biliary drainage is tabulated in Table 4 (Mauro et al. 2013).

Table 4 Equipment needed for PTBD

• Omnipaque 350 mgI/mL (as contrast media)
• 1% Lignocaine (as local anaesthesia)
• Midazolam and Fentanyl (as moderate sedation)
• Scalpel blade (for skin knit)
• 21G needle with stylet
• 0.018″ guidewire
• Coaxial introducer system, e.g. Neff Percutaneous Access set (Cook Medical, Bloomington, Ind.) or AccuStick set (Boston Scientific)
• 4Fr or 5Fr sheath
• 4Fr to 5Fr catheter (e.g. Berenstein, C2)
• Guidewires (e.g. 0.035″ hydrophilic wire, 0.035″ Amplatz Super stiff)
• 6–10 mm inflatable balloon catheters
• 8Fr and 10Fr biliary drains (e.g. Navarre)

8 Techniques

8.1 Biliary Access and Percutaneous Transhepatic Cholangiography (PTC)

Once the assessment and planning is done, either the right lower chest wall/upper abdomen (for right duct approach) or subcostal/subxiphoid area (for left duct approach) is cleaned and draped in a standard sterile fashion. Local subcutaneous anaesthesia is administered using 1% Lignocaine. The advantages and disadvantages of the right or left approach are summarized in Table 5 (Brown and Covey 2008).

The peripheral duct (based on the assessment of the prior imaging studies) is punctured with 20 or 21G needle under direct sonographic visualization (Fig. 4a). A through and through puncture of the duct is usually performed and needle is gently withdrawn until bile is easily aspirated into the syringe. Bile specimen is collected for microbiology. Thereafter, a cholangiogram is obtained by slow careful phasic injection of contrast. Care should be taken not to disengage the bile duct. Usually, the needle will move slightly deeper/posteriorly when the needle is connected to the contrast syringe, thus a slipped tip is helpful in avoiding inadvertent movement of the needle tip. If resistance is felt while injecting the contrast, the needle it should be slowly withdrawn until bile is aspirated and injection of contrast is then continued. It is important not to administer contrast volume more that the volume of fluid that was aspirated from the obstructed system to avoid forcing the bacteria from the obstructed biliary system into the bloodstream and causing septicaemia and intraprocedural septic shock (Brown and Covey 2008).

Puncturing the peripheral bile duct is safer than puncturing the central ducts (at the biliary hilum) where the presence of parallel vascular structures such as hepatic artery and portal vein increases the risk of bleeding. Moreover, access at the peripheral bile ducts allow sufficient length and side holes of the drain in the ductal system,

Table 5 Right versus left duct approach

	Right duct	Left duct
Fluoroscopic technique	• 11th intercostal space along mid-axillary line	• 3 finger breadths below xiphoid, with needle directed 30–45° postero-superiorly
Advantages	• Lesser radiation exposure to the operator • Safer as greater parenchyma available for access	• When right duct approach is precluded in situations like the presence of bowel loop anterior to right liver lobe, hilar tumour with extension up to secondary confluence causing isolation of right anterior and posterior sectoral ducts • Less ascites leak
Disadvantages	• Prone to leak in cases of ascites • Less comfortable for patients (drain in intercostal space)	• Increased radiation exposure to the operator

reducing the rate of peri-catheter leaks and reducing the length of the biliary stent from extruding into the liver parenchyma (Brown and Covey 2008; Sutter and Ryu 2015).

8.2 Percutaneous Transhepatic Biliary Drainage (PTBD)

After the contrast injection and cholangiography, a 0.018-inch introducer guidewire is gently advanced through the needle. The guidewire would follow the tract of a through and through puncture if it is pushed out of the needle. Therefore, it is advisable to bring the guidewire tip to end of needle and gently unsheathe the wire by slightly pulling back the needle. The guidewire is then gently directed into the target bile duct. Once sufficient length of the guidewire is advanced into the bile duct, the needle is exchanged for a coaxial system to upsize the 0.018-inch access guidewire to a 0.035 guidewire. The access is secured with vascular sheath. A directional catheter (Bernstein, Klumpke) and hydrophilic guidewire are used to cross the obstruction. After serial dilatation, internal-external multiple side hole biliary drainage catheter can be deployed over a stiffer guidewire (e.g. Amplatz wire). If difficulty is encountered in crossing the sites of obstruction, an external biliary drain can be temporarily deployed, for future attempt of internal-external PTBD insertion. External drain is sometimes favoured in cholangitic patients as prolonged manipulation of the obstructed biliary system can result in severe bacteraemia and septic shock (Sutter and Ryu 2015) (Fig. 4).

8.3 Percutaneous Biliary Stenting

Biliary stenting for palliation should aim to achieve adequate drainage for at least equal to or longer than the average life expectancy of the patients. The average life expectancy for patients of MBDO is reported to be 5.8–7.5 months (Gordon et al. 1992). As the techniques and devices have improved over the past two decades, now the average stent patency rate has improved to about 8.6 months (Maybody et al. 2009), making percutaneous metallic stents appropriate for palliation.

When there are signs of infection (i.e. cholangitis) or hints to suggest high risk of stent blockage (e.g. blood clots/haemobilia, stones or intraductal tumours visualized), percutaneous biliary stent placement should be avoided. For example, in cases of haemobilia or cholangitis, the procedurists can opt to first deploy a temporary external biliary drain or PTBD and arrange for future stenting once hemobilia or cholangitis has settled (Brown and Covey 2008).

Similar to PTBD, biliary access is obtained. Sheath cholangiogram is performed to determine the *length* and *extent* of bile duct obstruction to select an appropriate length and calibre of biliary stent. Over a guidewire, the stent is deployed across and several centimetres distal to the obstruction, but preferably not into duodenum to

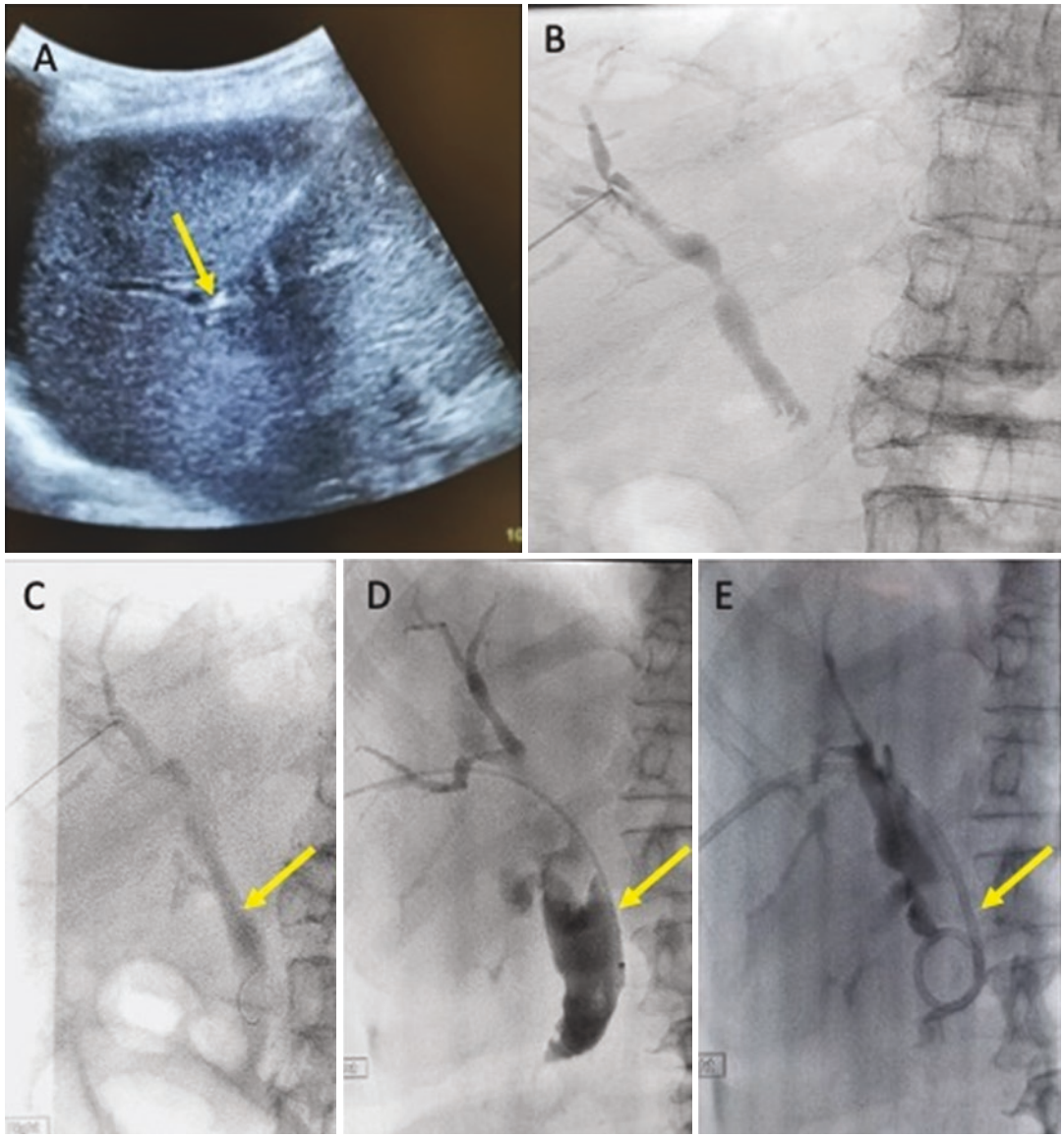

Fig. 4 Percutaneous transhepatic biliary drainage (PTBD). (**a**) The dilated right-sided ducts are accessed by a 21G needle under sonographic visualization (arrow). (**b**) Biliary entry is confirmed by gentle contrast injection. (**c**, **d**) Over a 0.018-inch guidewire (arrow, **c**), the access is gradually upsized to accommodate a 6F outer sheath (arrow, **d**) and cholangiogram obtained. (**e**) Finally, an 8F external drainage catheter (arrow) is inserted

preserve the function of the sphincter of Oddi. Post-sheath cholangiogram is performed to check for antegrade passage of contrast into the duodenum (Sutter and Ryu 2015) (Fig. 5).

In Bismuth *type 1* obstruction, *single* stent placement is adequate. In Bismuth *type 2* obstruction, *2 stents* are preferred (Brown and Covey 2008). There are two ways in deploying 2 stents in this setting. For example, *T configuration* involves deploying the first stent connecting the ipsilateral to contralateral bile ducts; and the second stent draining the ipsilateral bile duct

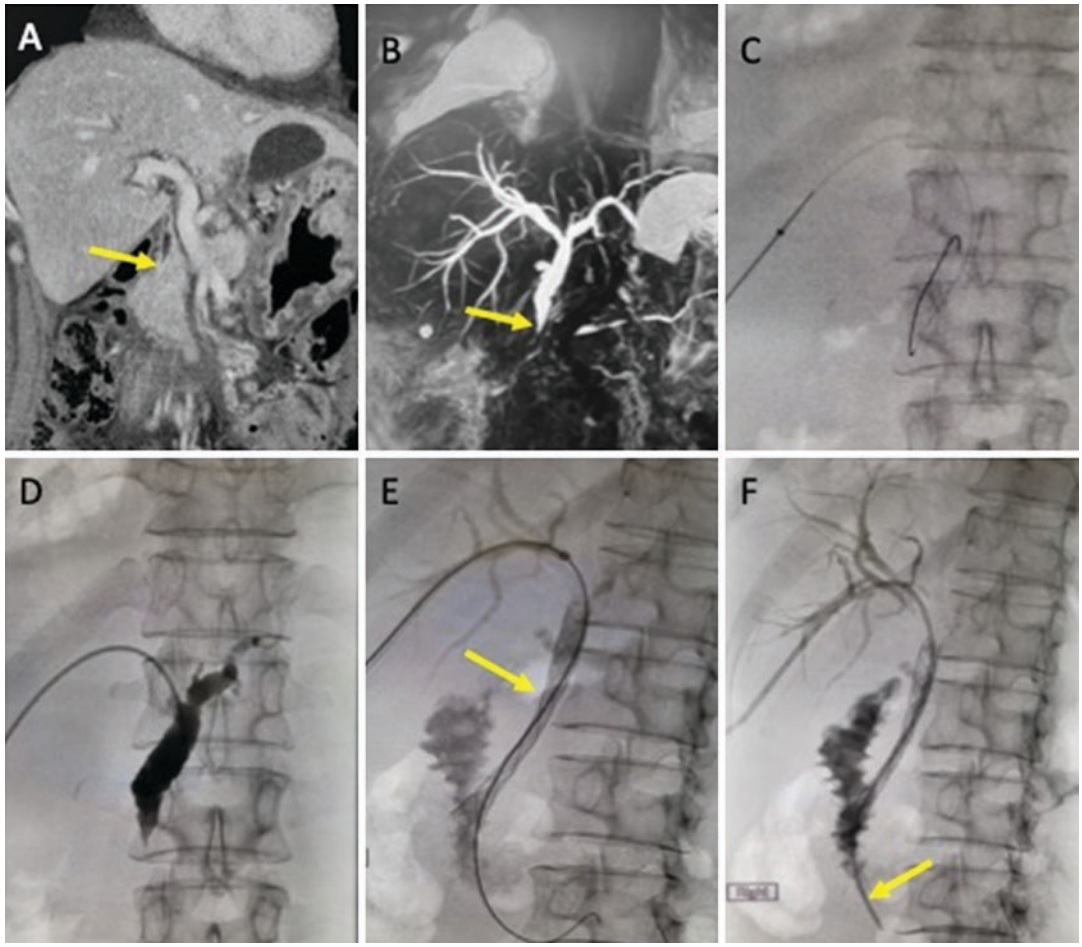

Fig. 5 Percutaneous biliary stenting. (**a**) Contrast-enhanced coronal CT image shows abnormal wall thickening and enhancement from a malignant stricture (arrow), suspicious for cholangiocarcinoma. (**b**) 3D MIP image from a magnetic resonance cholangiopancreatography (MRCP) study dilated ducts and obstruction from the stricture (arrow). (**c**) Peripheral biliary access is obtained through a right posterior sectoral duct. (**d**) Cholangiogram depicts distal common bile duct obstruction. (**e**) An uncovered metallic stent (arrow) is deployed across the site of obstruction with about 1 cm of stent projecting into the duodenum. (**f**) Completion cholangiogram demonstrates good drainage with no stasis of contrast in the common bile duct. (**f**) A temporary safety catheter (arrow) is usually left within the stent to maintain access for 24–48 hours

to the CBD (Brown and Covey 2008). Whereas, in *Y configuration*, the first access is obtained from the right hepatic duct and the second access is obtained from the left hepatic duct, and both stents are deployed side-by-side in parallel fashion or stent-in-stent configuration. Y configuration is believed to be better option, as it offers higher patency rate (Brown and Covey 2008). If the secondary confluences on both sides are involved, more stents are needed, and they can be deployed using stent-in-stent method (Fig. 6) (Brown and Covey 2008). Readers can refer back to the summary in Table 3.

8.3.1 Plastic Versus Metallic Stents

The evidence supporting the superiority of metallic stents has been established and widely pub-

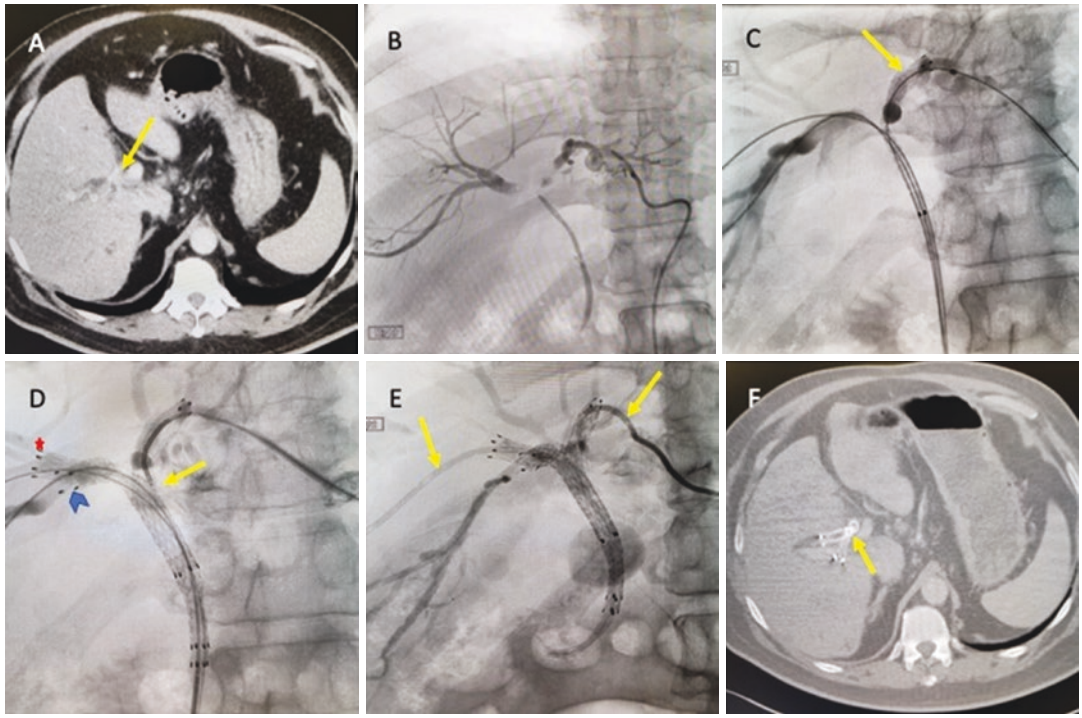

Fig. 6 Percutaneous biliary stenting (multiple stents-in-stent configuration). (**a**) Contrast-enhanced axial CT image shows enhancing soft tissue infiltrating the hilum of intrahepatic bile ducts with involvement of the secondary confluence on the right side (arrow), consistent with a Bismuth type 3 lesion. (**b**) Cholangiogram confirms the findings on CT. (**c**) The first stent is deployed across the left hepatic duct (arrow). (**d**) Second stent (blue arrowhead) was deployed from the right posterior hepatic into the left ductal stent (arrow), and finally the third stent (red star) was deployed across the right anterior sectoral duct into the right posterior sectoral ductal stent. The catheter tip is placed at the stent wall to gain access into the stent lumen and struts are broken by balloon dilatation to facilitate stent deployment and finally create a common cavity. (**e**) Post-stenting temporary external biliary drainages (arrows) are inserted. (**f**) Post-procedure axial CT image shows good position of the stents with stent-in-stent configuration (arrow)

lished. The metallic stents offer longer patency, fewer re-intervention rates and overall better survival compared to the plastic stents as confirmed by recent series of meta-analyses. The lower long-term occlusion rates of metallic stents compared with plastic stents are observed in hilar as well as distal malignant obstruction (Almadi et al. 2017; Sawas et al. 2015).

8.3.2 Covered Versus Bare (Uncovered) Metallic Stents

The main limitation of bare metallic stents is the tendency for tumour ingrowth with resultant stent occlusion. Covered stents are subsequently designed with the intention to overcome this problem in distal biliary obstruction. The covered stents with covering materials made from expanded-polytetrafluoroethylene/fluorinated ethylene propylene (ePTFE/FEP) showed promising results in some prospective studies and with longer patency period and fewer re-interventions than bare stents (Krokidis et al. 2011). The lesser occlusion rates, however, failed to show any statistically significant difference in the survival benefit as concluded by recent meta-analysis (Moole et al. 2016). The same study reported increased odds of migration and pancreatitis with covered stents compared to uncovered stents (Moole et al. 2016). Migration was mainly noted in the studies where the stents without fixation barbs were used and thus as such is not a major concern with newer current generation stents.

Primarily envisioned to prevent tumour ingrowth, covered metallic stents suffer from tumour overgrowth which affect their overall patency (Tringali et al. 2018).

8.3.3 Drug Eluting Stents and Intraductal Ablation

Drug delivery through the stents akin to vascular disease had been tried for malignant biliary obstruction. Various drug-eluting stents incorporated with chemotherapeutic agents such carboplatin, paclitaxel or gemcitabine have been utilized in management of MBDO. To date, however, the drug-eluting stents do not appear to offer an advantage in the palliation of malignant biliary disease, at least not in terms of stent patency (Krokidis and Hatzidakis 2014).

Other exciting yet not well established minimally invasive treatment for MBDO is intraductal radiofrequency ablation (RFA). RFA uses high frequency rapidly alternating electric current that causes vibrational water molecule movement in the ablated tissue, which then transform into frictional heat deposited in biological tissue and causes tumour necrosis. In the liver, the use of RFA is well established. The first biliary intraductal RFA use in human trial was reported in 2011, involving 22 patients with unresectable bile duct or pancreatic cancers. Indications for biliary RFA described in literature include palliative treatment of malignant biliary strictures, ablating ingrowth of blocked metal stents, prolonging stent patency, ablating residual adenomatous tissue after endoscopic ampullectomy. Existing evidence from retrospective studies suggest a beneficial effect on survival and stent patency, however, good quality evidence by means of prospective studies or randomized trials is lacking (Auriemma et al. 2019).

8.4 Recurrent Occlusion After Stent Placement

Should a percutaneous placed biliary stents become occluded, there are few options available. But, none of the options can be claimed as the best method for all patients. The best outcome is usually based on a case-to-case basis, with the priority first given to the patients' preference. It should always be borne in mind that percutaneous intervention in MBDO is for palliative purpose, thus adjusting ones threshold to be not too aggressive until complications become unjustified. As a general rule, if stents are unfortunately occluded, the problem can first be addressed endoscopically, unless anatomically challenging. In general, if the stent occlusion happens after 6 months of placement and cholangiography findings are favourable, repeated percutaneous stenting can be tried (Fig. 7). If less than 6 months, percutaneous drainage should be performed (Brown and Covey 2008).

9 Post-procedural Care

After percutaneous biliary intervention, the patients are often instructed to follow standard post-procedure instructions (Table 6) (David 2016).

10 Outcomes

The technical success rate of access to dilated bile ducts in MBDO is near 100%; while the success rate of access to non-dilated bile ducts is reported to be greater than 70%, though non-dilated bile ducts are rarely encountered in MBDO. The clinical outcome of PTBD vary widely according to the indication, location and extent of MBDO, functional liver parenchyma and comorbidities. In general, PTBD is effective in addressing pruritus and cholangitis. Metallic biliary stents have a median patency of 6–9 months (Raymond and Anne 2013), similar to the life expectancy of patients with MBDO.

11 Complications

The procedure-related mortality from percutaneous biliary interventions is about 3%, with major complications rate of approximately 5% (Saad et al. 2010). The most common complication is septicaemia. Even with prophylactic antibiotics coverage, acute sepsis can still occur. Hence,

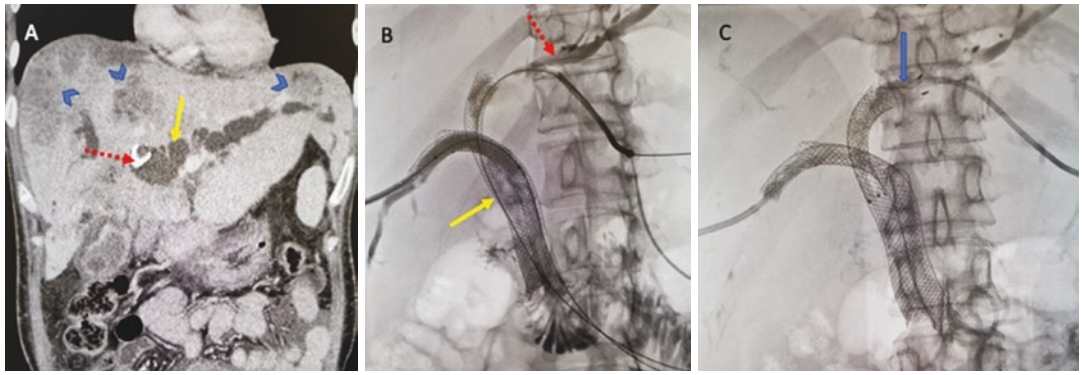

Fig. 7 Re-intervention in blocked stents. (**a**) Contrast-enhanced coronal CT image shows marked left biliary dilatation (solid arrow) 6 weeks after deployment of covered bilateral stents (red dotted arrow) for malignant infiltrative lesion at the hilum. Multiple liver metastases (blue arrowheads) are also seen. (**b**) Cholangiograms from bilateral access demonstrate poor drainage through the left stent (solid arrow) with stasis of contrast in segmental left ducts (red dotted arrows). (**c**) Improved drainage following extension and re-alignment of left biliary stenting using an uncovered metallic stent (blue arrow)

Table 6 Post-procedure care

1.	Complete rest in bed (CRIB) × 6 hours
2.	Vital signs monitoring ¼ hourly × 1 hour, hourly × 5 hours, 4-hourly thereafter
3.	Monitor for signs and symptoms of bleeding and cholangitis
4.	Drain under free drainage
5.	Check the trend of liver function test (LFT)
6.	Check the results of microbiology from bile specimen
7.	Standard catheter, skin and dressing care
8.	Education to the caregivers on how to monitor for post-procedure complications (e.g. infection, bleeding)
9.	Trial of capping (for PTBD) if planning for percutaneous stent placement
10.	To arrange for stent placement when haemobilia has cleared and cholangitis has resolved

caution should be taken when contrast is injected during cholangiography. Bleeding can occur if vascular structures such as are injured. If it involves branches of portal vein or hepatic veins, management is usually conservative. However, if hepatic arteries are injured, the patients may require emergency intervention (e.g. embolization) though injury to the hepatic arteries are relatively less common (Sutter and Ryu 2015).

Table 7 Major complications of PTC

Major complication	Reported rate	Suggested specific threshold
Haemorrhage, sepsis, cholangitis, bile leak or pneumothorax	2%	4%

Patients undergoing right-sided approach especially via the intercostal route may experience pain, postulated to be attributed to intercostal nerves and periosteal irritation. If the puncture is too high, pleura may be transgressed, and can lead to pneumothorax or haemothorax (reported to be 0.5–2%). Peri-catheter leak is slightly more common for right-sided drain, given the more dependent position of the intercostal approach. Having said that left-sided catheter can also leak. Once this happens, peri-catheter leak can contribute to negative effect on the quality of life in these patients. Catheter upsize can potentially help to obturate patulous transhepatic track if it occurs (Sutter and Ryu 2015). Major complications from PTC (Table 7) and PTBD (Table 8) were summarized below (Saad et al. 2010).

Table 8 Major complications of PTBD

Major complication	Reported rate	Suggested specific threshold
Intraprocedural		
(a) Haemorrhage	2.5%	5%
(b) Sepsis	2.5%	5%
(c) Infective/inflammatory (e.g. abscess, peritonitis, cholecystitis, pancreatitis)	1.2%	5%
(d) Pleural	0.5%	2%
(e) Death	1.7%	3%
Post-procedural		
(a) Inadvertent catheter discontinuation requiring de novo PTC, death and / or surgery	[a]	[a]

[a]It is a recognized post-procedural complication, but lack of clear consensus in the literature on the rate of this complication

12 Conclusion

Interventional radiology play an important role in MBDO. Pre-procedure planning is essential to achieve the goal of optimal biliary drainage with the least number of drains or stents. Gentle handling during the procedure can minimize procedure-related complications. Our involvement plays a vital role in ensuring a smooth palliative care and better quality of life of these patients.

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Obstruction Solutions for Kidneys and Urinary Bladder

Tan Hsien Khai

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Abstract

Malignancies affecting the urinary system are being encountered with increasing frequency. A commonly encountered scenario is obstruction of the upper urinary tract as a consequence of advance malignancies. Here, the role of palliative therapy takes on an increasing importance in delivering optimal care in ensuring best quality of life for patients. Interventional radiology (IR) in this instance offers the option for urinary diversion through procedures, which may benefit the patients, and thus represents an important facet of a multidisciplinary team in managing such conditions. This chapter will focus on available solutions, in managing obstructions of the kidneys and urinary bladder.

T. Hsien Khai (✉)
Khoo Teck Puat Hostpital, Singapore, Singapore
e-mail: tan.hsien.khai@ktph.com.sg

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_24

1 Introduction

Hydronephrosis can be caused by intrinsic obstruction or extrinsic compression of the urinary tract from the primary tumour or associated retroperitoneal adenopathy. Examples include neoplastic processes of urologic, gynaecological or gastrointestinal (GI) origin, and adverse effects associated with treatment such as radiotherapy. Direct invasion of a urothelial tumour or invasion of the ureter by bladder, prostate, cervical or colorectal tumours are examples of an intrinsic obstruction, while strictures, scarring and adhesions form the sequelae of radiotherapy.

Hydronephrosis is considered an indicator of morbidity and reduced survival in cervical and GI malignancies (Radecka et al. 2006; Pradhan et al. 2011; Migita et al. 2011). Urinary diversion as a form of palliation will prevent further deterioration of renal function (Shekarriz et al. 1999; Wong et al. 2007) thereby prolonging survival. The aim is to prevent death due to complications of uraemia, and if possible, optimizes patient for additional chemo- or radiotherapy (Wilson et al. 2005; Kouba et al. 2008).

Solutions for upper tract diversion include percutaneous nephrostomy (PCN) and antegrade ureteric stenting, while urethral and bladder outlet obstruction can be managed with suprapubic catheter placement.

2 Percutaneous Nephrostomy

The principle of percutaneous nephrostomy is to access the collecting system through a relatively avascular zone thereby establishing a form of urinary diversion. This can then be extended with antegrade ureteric stenting, if indicated.

3 Anatomy

The renal artery divides into the anterior and posterior branches. This division gives rise to a zone of relative avascularity along the posterolateral aspect of the kidney, known as Brodel bloodless line of incision (Zagoria and Dyer 1999; Papanicolaou 1995).

4 Patient Preparation

A discussion as to the indication and complications of the procedure should be carried out followed by an informed consent. The potential need for conscious sedation is also conveyed to the patient. As a routine, screening or bleeding diathesis including a full blood count and a coagulation profile are obtained. Prophylactic antibiotic coverage is also initiated prior to the patient leaving the ward for the intervention suite. A review of any relevant form of imaging should also be performed prior to start of procedure. This is followed by initial sonographic visualization and evaluation of the collecting system prior to cleaning.

5 Technique

Procedure is performed with the patient prone. Pre-procedure ultrasound is performed to evaluate for hydronephrosis (Fig. 1). The back and flank are cleaned in the usual sterile technique as per institution protocol. A posterolateral approach is taken under ultrasound guidance, beginning with infiltration of 1% lignocaine from skin to the renal capsule. This is followed by a skin incision made in approximate size of the intended drainage catheter. An 18-gauge, 21-gauge, or 22-gauge needle is then inserted along the same trajectory, depending on the preference of the interventionist, under ultrasound guidance. Access into the collecting system is

Fig. 1 Pre-procedure ultrasound performed to evaluate degree of hydronephrosis

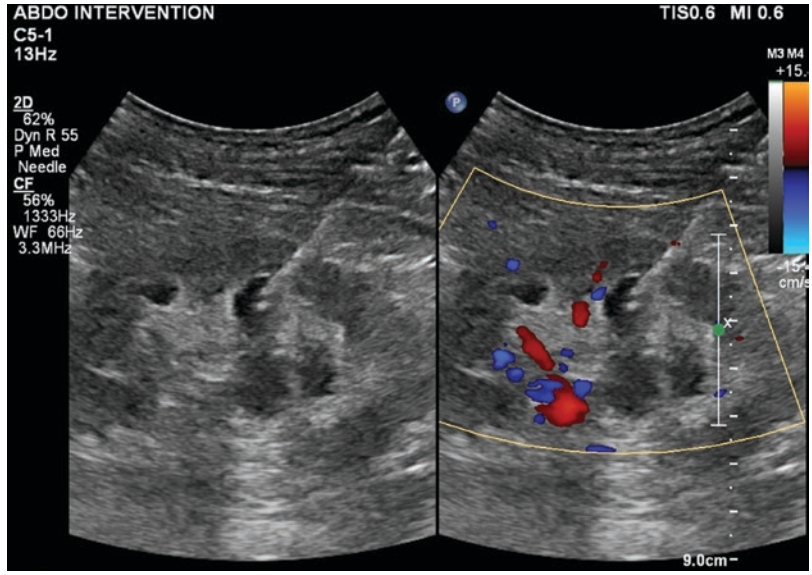

Fig. 2 Placement of an 18-gauge needle into the mid-pole calyx of the left kidney. Image on the left depicts the needle traversing a relatively avascular plane (Brodel line)

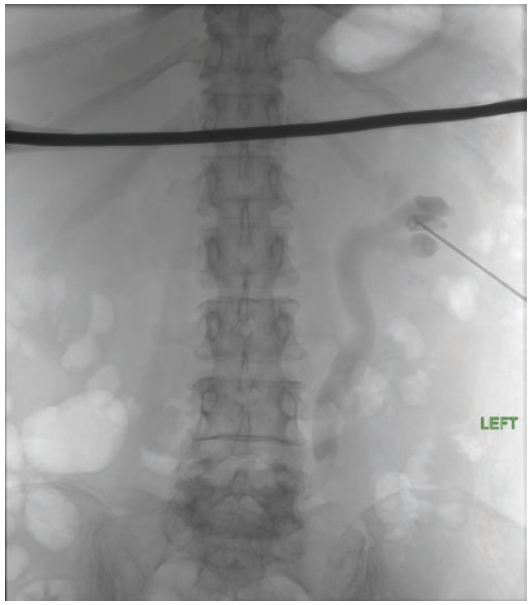

Fig. 3 Diluted water-soluble contrast is injected to confirm position of needle and opacify the collecting system

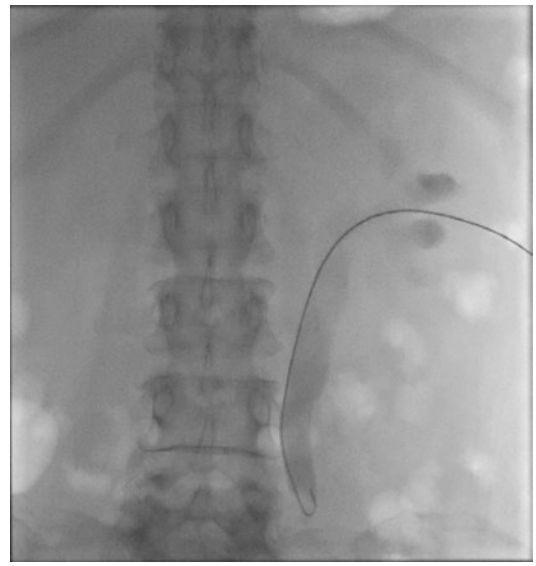

Fig. 4 Access secured with an 0.035 inch working wire

confirmed under direct vision (Fig. 2). The stylet of the needle is then removed and followed by aspiration of urine, which is collected and sent for analysis. The procedure is then guided via continuous fluoroscopy, where contrast is injected to opacify the collecting system (Fig. 3). The 21- or 22-gauge needles are accompanied by a 0.018-inch wire which is inserted to secure access. The needle is then removed and exchanged for accompanying transition dilators, which can accommodate a larger, usually 0.035-inch working wire (Fig. 4). This is followed by dilatation of the tract to accommodate a drainage catheter. Serial dilatation would be required for 10–14 French prior to insertion of drainage catheters. Drainage catheters are usually the

Fig. 5 8-French pigtail, self-locking catheter is finally deployed and guidewire removed

Fig. 6 Injected contrast was fully aspirated to confirm optimal position and adequate drainage of the collection system

self-retaining or locking catheters to decrease the incidence of inadvertent dislodgment. As part of an initial placement, these catheters are inserted with a metal stiffener inside.

Catheters of 8–10 F are usually sufficient for drainage (Fig. 5). Larger catheters (12–14 F) may be necessary in cases of gross haematuria. Position of the catheter is then confirmed with injection of contrast, followed by decompression of the collecting system (Fig. 6). The latter is indicative of optimal catheter placement. The catheter is then anchored to skin with sutures.

6 Antegrade Ureteric Stenting

A common extension of nephrostomy is ureteric stenting. The stent is deployed from an antegrade approach utilizing the primary nephrostomy access. The purpose of the stent is to cross the obstructed segment.

7 Technique

When performed after as a follow-up to percutaneous nephrostomy, the nephrostomy catheter is removed over a guidewire after cutting the hub. The wire is then exchanged for a hydrophilic wire, which is manipulated into the pelvi-ureteric junction into the ureter, assisted by an angiographic catheter. The site obstruction is then negotiated, and the wire is advanced into the urinary bladder. At this point, options for balloon dilatation may be considered (Banner 1998). The appropriate length of the stent is then estimated. The stent is inserted with a pusher, which places the distal loop within the urinary bladder and the proximal loop within the renal pelvis (Figs. 7 and 8). A safety nephrostomy catheter is finally placed for 24 h after stenting (Fig. 9). This catheter is clamped to determine adequate drainage has been accomplished via the stent. The nephrostomy tube should be removed with fluoroscopic assistance to ensure the proximal loop of the stent is not inadvertently caught in the loop of the nephrostomy tube (Banner 1998).

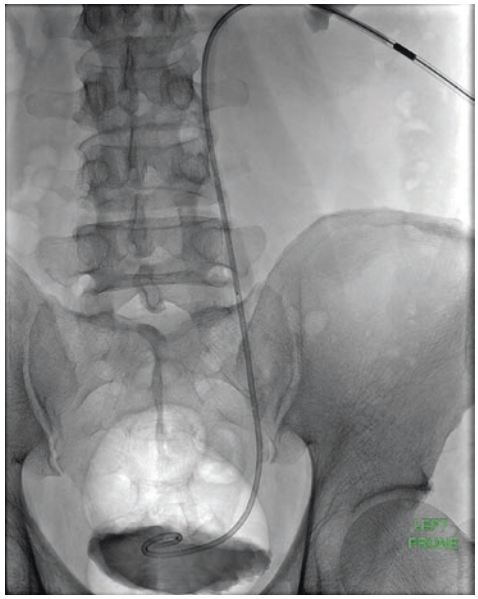

Fig. 7 Antegrade ureteric stent placement, with the distal loop being formed in the urinary bladder. A pusher is used to manoeuvre the stent into place, arrow

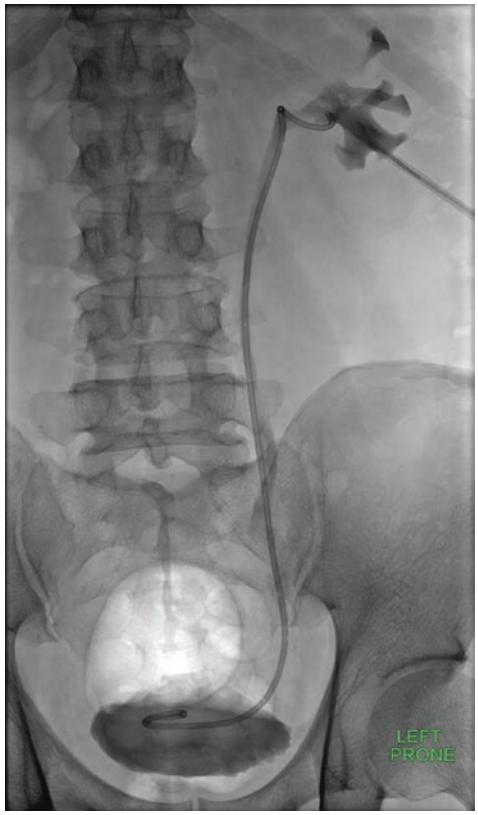

Fig. 8 The proximal loop of the ureteric stent is formed in the renal pelvis

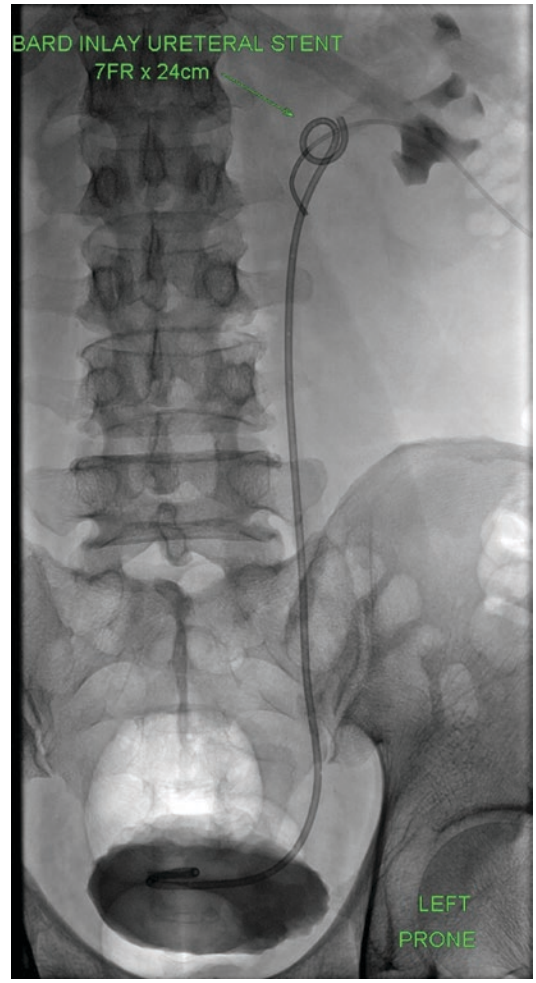

Fig. 9 Final position of the ureteric stent with a nephrostomy safety catheter in place, arrowhead

8 Complications of Percutaneous Nephrostomy

The mortality rate for percutaneous nephrostomy is relatively low and ranges from 0.046 to 0.3% (Segura et al. 1985; Lang 1987; Lee et al. 1987; Stables 1982). While transient haematuria occurs in virtually every patient, severe bleeding that requires transfusion or intervention occurs in 1–3% of patients (Farrell and Hicks 1997). In most cases, the bleeding that occurs at the time of percutaneous nephrostomy can be controlled by tamponade afforded by the nephrostomy catheter (Ferral et al. 1994).

However, when significant blood loss occurs, cross-sectional imaging followed by angiographic evaluation should be employed to determine the source of bleed, which is usually managed by embolization. These injuries include the formation of pseudoaneurysm or arteriovenous fistula.

Risk of sepsis is 1–2.5% (Stables 1982; Bjarnason et al. 1994).

Inadvertent injury to adjacent organs, such as the colon (Hopper et al. 1987), and pneumothorax or hydropneumothorax have been known to occur (Narasimham et al. 1991).

9 Image-Guided Suprapubic Catheter Placement

Suprapubic catheter placement is usually performed by urologists and surgeons. Nonetheless, there have been articles depicting the procedure being performed by interventional radiologists (Lee et al. 1993; Papanicolaou et al. 1989). The authors describe insertion of the suprapubic catheter via Seldinger technique under image guidance. The procedure may be performed under ultrasound—fluoroscopic or CT guidance. Catheters used include self-retaining pigtail catheters (8–14 French) or Foley catheters (12–14 French).

10 Technique

The urinary bladder is filled with diluted contrast medium via an existing Foley catheter. The distension enables the bladder to approximate the anterior abdominal wall while displacing the small bowel loops. Ultrasound is then performed to ensure that there is no intervening vascular structures or bowel loops. Patient is then prepared and cleaned in the usual sterile manner.

The primary puncture site is chosen, lateral to the midline, superior to the symphysis pubis. One percent lidocaine is then infiltrated from the skin to the urinary bladder.

An 18-gauge needle is then inserted under ultrasound guidance. Urine is aspirated to confirm needle placement. Access is then secured with a stiff Amplatz guidewire followed by serial dilatations performed under fluoroscopic guidance to accommodate the catheter.

11 Complications

Complications of suprapubic catheter insertion are minor and include infection, haemorrhage, and bowel injury. Minor complications occurred in 7.2% (42/583) of primary suprapubic tube insertions (Cronin et al. 2011). The same authors also documented a major complication where there was inadvertent small bowel injury secondary to adhesions to the urinary bladder as a consequence of previous laparotomy.

12 Conclusion

There is no clear outcome as to the superiority of percutaneous nephrostomy versus ureteric stenting with respect to complications and quality of life. Thus, management is based on a case-by-case basis following a multidisciplinary consensus, which involves the patients and their families and the primary team (Hsu et al. 2016). Image-guided percutaneous suprapubic catheter placement can also be employed in distal obstruction involving the urethra and urinary bladder with high success rates (Cronin et al. 2011).

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Role of IR in Large Bowel Obstruction

John Francis Leahy

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1 Introduction

Colorectal cancer is one of the most common cancers worldwide (van Hooft et al. 2014), the third most common cancer in the UK (Sagar 2016), and North America (Borowiec et al. 2016) and the second most common cause of cancer-related deaths. Up to 20% of cases develop obstruction (Borowiec et al. 2016), 8–13% initially presenting with colonic obstruction (van Hooft et al. 2014; Sagar 2016). Surgery is the mainstay of treatment. There are several possible surgical approaches, including a single step curative resection with primary anastomosis, a two-stage procedure with initial stoma for surgical decompression followed by subsequent anastomosis or palliative stoma formation (De Simone et al. 2017). However, surgery in obstructed patients carries risks of morbidity (18–46%) and mortality (16–38%) (Borowiec et al. 2016).

Expanding metal stents have been inserted since the early 1990s (Dohmoto et al. 1997). They may be inserted using endoscopy, fluoroscopy, or a combination of the two. The aim of

J. F. Leahy (✉)
Sandwell and West Birmingham Hospitals NHS Trust, West Bromwich, UK
e-mail: John.leahy@nhs.net

© Springer Nature Switzerland AG 2021

P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_25

stenting may either be as the first step to decompress the bowel and allow later definitive surgery on a semi-elective basis (often described as a "bridge to surgery") or as a stand-alone procedure, intended to allow chemotherapy or radiotherapy, or purely as palliation. This chapter describes the technique for stent insertion used in the interventional radiology department of a large general hospital in the UK and discusses the outcomes and the place of stenting in the management of these cases.

2 Patient Selection

The indication for stenting is malignant large bowel obstruction, there being no role in prophylaxis (van Hooft et al. 2014; Sagar 2016). The absolute contraindication is existing perforation (van Hooft et al. 2014; de Gregorio et al. 2004).

Benign strictures of the colon need separate consideration and results of stenting are generally poorer, with a higher risk of perforation (van Hooft et al. 2014; Sagar 2016). Stenting in colonic obstruction due to extrinsic compression is possible but may associated with worse outcomes although the evidence is mixed (van Hooft et al. 2014; Sagar 2016).

Cases with complete, as opposed to subacute, obstruction may be more problematical. Some studies conclude that stenting of complete obstructions is associated with higher risk of complications such as perforation (Small et al. 2010).

As regards the site of the obstructing tumour, some authors are happy to include right colonic lesions (de Gregorio et al. 2004; Kim et al. 2013), but the majority of studies are limited to stenting of the left colon (van Hooft et al. 2014; Sagar 2016). Rectal lesions are excluded by all authors, as low placement of a stent is more likely to result in pain and tenesmus. Stent insertion in tortuous areas of bowel is more likely to be technically difficult (de Gregorio et al. 2004; Kim et al. 2013).

Right colonic lesions are more likely to require the use of endoscopy (de Gregorio et al. 2004).

3 Technique

3.1 Preparation

A phosphate enema may be helpful, but is not usually essential (van Hooft et al. 2014). The procedure is embarrassing, rather than painful, and sedation is optional. It is useful to explain to the patient while obtaining consent that gas and liquid will inevitably be passed during the procedure, in order to lessen the patient's anxieties. Support from a nurse during the procedure is extremely useful.

Fluoroscopy equipment with a C arm and high-quality, low-dose imaging is essential. A tilting table top is not required. It is often helpful to cover the equipment couch with disposable sheets (unused sheets from previously opened sterile packs serve very well), as well as covering the image intensifier and any lead shields. It is also helpful to wear a surgical gown and gloves. The purpose in this case is not that the procedure is aseptic, but rather to reduce the need for cleaning of equipment and lead coats afterwards.

The patient ought to have undergone CT scanning to diagnose the obstruction, define the site of obstruction, establish the cause, and provide local and distant staging (van Hooft et al. 2014). The most recent CT scan is also extremely useful for reference and should be displayed in the procedure room to aid navigation.

3.2 Patient Positioning

Assuming the stent placement will be under fluoroscopy alone, our usual practice is to place the patient prone. A lateral position may be more comfortable, but the patient is more likely to move, or fall off the table if it is narrow. Standard monitoring (pulse, BP, pulse oximetry, and ECG) is used.

3.3 Disposable Equipment

Usually, a simple catheter shape, e.g. left vertebral is used. More complex shapes are reserved

for particular problems. The ideal catheter length is 65–100 cm. 5F gives adequate torque without excessive stiffness. Catheters with radio opaque tips are preferred, as these allow use of lower radiation doses. Many authors advocate the use of a Terumo guidewire (de Gregorio et al. 2004; Kim et al. 2013), but a Rosen guidewire with a narrow J tip also has advantages. The radio opacity of the tip of the Terumo is poor, and perforation is less likely with a J tip. A 260 cm ultra stiff J tip guidewire will be needed to introduce the stent introducer and is sometimes useful during catheter manipulation or to straighten tortuous loops of bowel. Finally, the catheter is premounted through a long 6F vascular sheath, so that this can be introduced over the catheter to reduce loop formation in the catheter as it advances. At the author's institution, an Egis Niti S uncovered "double bare" stent is usually employed for over the wire procedures.

3.4 Procedure

Some authors advocate performing an initial limited contrast enema (de Gregorio et al. 2004). However, excessive contrast can become confusing and obscure guidewire position, particularly if it accumulates in dependent areas of bowel. Instead, both negative contrast (air) and positive contrast (dilute iodinated contrast) can be injected via the catheter as progress is made along the bowel. Warm tap water can be used to lubricate the guidewires and catheters and to dilute the contrast.

The stages of stent insertion are illustrated in Fig. 1.

After lubrication with lignocaine gel, the catheter is introduced via the anus and advanced proximally under antero posterior fluoroscopic control; in most cases, no guidewire is needed at this stage. Air is injected via the catheter to outline and distend the rectosigmoid. Once the catheter reaches the apex of the rectum small injections of positive contrast to outline the sigmoid, and use of the guidewire to stiffen the catheter, become essential. However, it is often useful to advance the catheter alone in front of the guidewire tip. Because the rectum is usually capacious, there is a particular risk that loops of guidewire and/or catheter may be formed; this can be avoided by careful technique and by advancing the sheath over the catheter to stiffen the system once the catheter tip has progressed into the sigmoid. The sigmoid loop in particular is mobile and may lengthen or shorten. During an exchange of guidewire, particularly during the introduction of a stiff guidewire, the additional stiffness tends to widen loops and lengthen the bowel. The tip of the catheter may retract several centimetres, and this should be borne in mind before changing wires. The softer guidewire is therefore preferred in most circumstances to avoid inadvertent catheter retraction. When partial withdrawal of the catheter is required, a guidewire should be in place because the catheter may suddenly retract much further than was intended. Progress is often characterised by a period of frustration, followed by a sudden advance of the catheter and wire of 10 cm or more before reaching the next bend or obstruction (Fig. 1a, b).

There is often periodic limited peristalsis and passage of liquid and gas through the bowel loops and anus, but occasionally there can be a considerable movement of the bowel with passage of a large quantity of liquid faeces. This will force the catheter and guidewire out of the patient unless the catheter is held firmly at the anus; at this moment full gowning and well-fitting surgical gloves will be appreciated by the operator. The position of the bowel loops may be considerably changed afterwards, and as they have emptied and shortened there may be an opportunity to make more rapid progress if the catheter has remained in situ.

Fluoroscopy is used in the lateral, AP, and oblique planes as required. It is very useful to store fluoroscopic loops of the contrast injections, as these may demonstrate the presence of loops or bends which are subsequently obscured by contrast. Fluoroscopy times are long, and careful coning is required to limit the radiation dose. Formal "spot" image acquisitions are reserved for particular circumstances, e.g. if there is faint contrast opacification of the track through

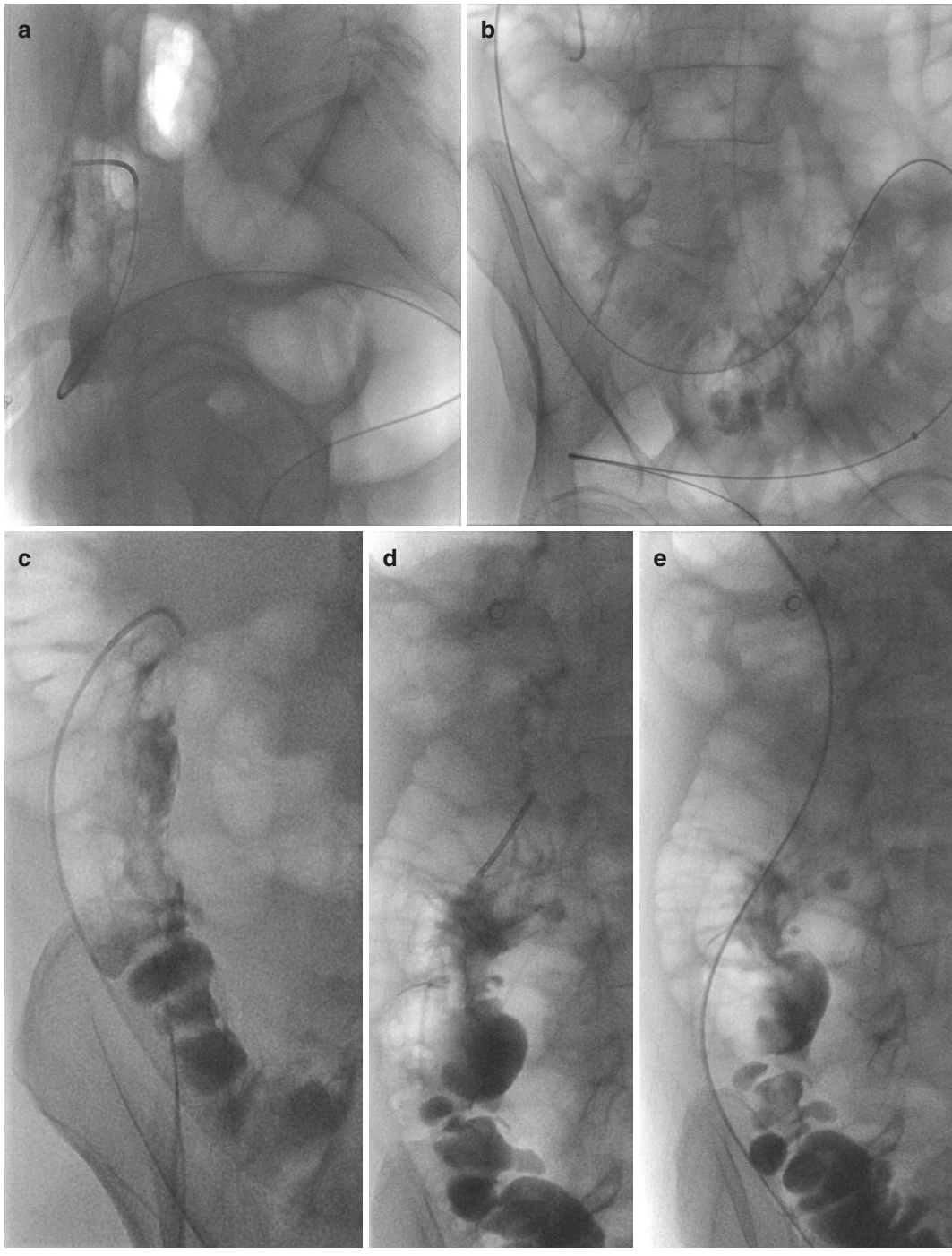

Fig. 1 Insertion of a stent in a lesion in the ascending colon. (**a**) The catheter has been introduced into the mid sigmoid. Air has been the predominant contrast medium so far. (**b**) The tip of the catheter is now coiled below the stenosis in the ascending colon. The tip of the sheath, recognised by its radio opaque marker, is the distal sigmoid. (**c**) The tip of the catheter lies distally within the tumour, but the course of the catheter is peripheral to the main lumen. The occluding lesion cannot be crossed from this position. (**d**) The catheter has been withdrawn and re-advanced medially through the tumour. Contrast now delineates the path through the stricture. (**e**) The catheter and guidewire have been advanced considerably beyond the stenosis. (**f**) The tip of the sheath now lies above the stenosis. Two wires are *in situ*. (**g**) A formal spot acquisition demonstrates the lesion after contrast and air are introduced. (**h**) The stent has been deployed in a satisfactory position

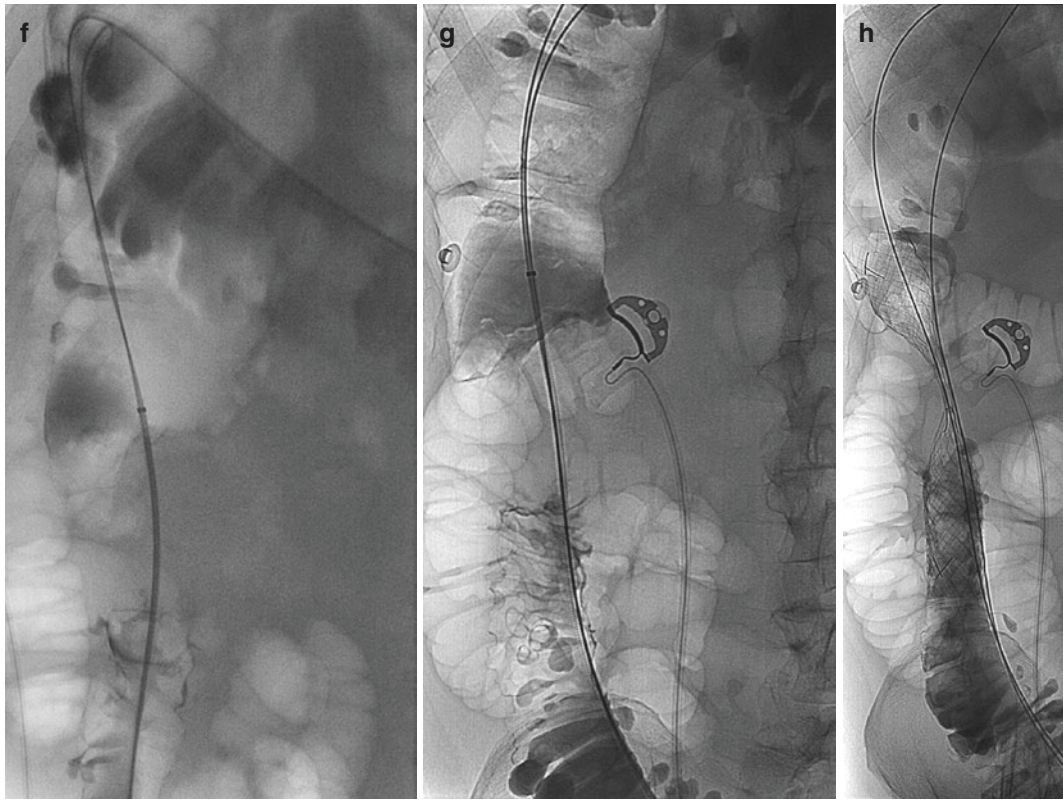

Fig. 1 (continued)

a tumour, or to visualise the position of the stent during deployment.

Crossing the stenosing lesion once it has been reached is usually challenging. Introduction of small quantities of dilute contrast may indicate the correct passage, or at least the entrance to it. There will usually be recesses at the margin of the tumour, and so progress in the expected direction does not always indicate that the lumen has been entered (Fig. 1c). It may be necessary to withdraw the catheter and re-advance it through the centre of the lesion (Fig. 1d). If the guidewire and catheter do not cross the lesion, contrast may opacify the track. Usually, the stenosis may be crossed using the same catheter and J guidewire, but a steerable hydrophilic wire is sometimes useful if there is difficulty.

Once the lesion is crossed, the guidewire and catheter are advanced a considerable distance into the proximal bowel, ideally to the splenic flexure, or even the transverse colon (Fig. 1e). This confirms correct positioning and allows some latitude when replacing the soft guidewire with the long ultra stiff wire. The sheath is then advanced over the catheter/guidewire, ideally so that its tip lies proximal to the stenosis. A second guidewire can then be introduced through the sheath to stiffen the system further (Fig. 1f). It is preferable to straighten the sigmoid loop prior to stent introduction and usually this is possible by retraction and then careful re-advancement of the sheath over the two wires. The anatomy of the lesion should be delineated by injection of dilute contrast above and below the stenosis through the sheath, this being a point at which a high-quality image should be obtained for reference after stent deployment (Fig. 1g). The length of the stenosis can be measured by advancing the sheath through the lesion under fluoroscopy while recording the distance on the guidewires outside the patient. There is no advantage in balloon dilation of the stricturing lesion before or after stenting, and dilation is associated with a higher incidence of perforation (van Hooft et al. 2014; Sagar 2016;

de Gregorio et al. 2004; Small et al. 2010). Biopsy of the lesion at this point, using forceps introduced via the sheath, has been described (de Gregorio et al. 2004).

The sheath is removed and the stent advanced over the long ultra stiff guidewire. The stent introducer is lubricated with gel. If the path remains tortuous despite attempts at straightening, it is useful to make a gentle curve in the stent introducer to aid passage around the bends. There may be some discomfort as the stent introducer traverses the loops. During deployment, there will be a sudden reversal of the pressure need to keep correct positioning; initially, it is often necessary to keep a steady inward pressure to prevent the stent introducer being expelled. Once deployment has started the stent is carried into the patient and the operator must maintain tension to prevent too proximal a position. After deployment, there is often rapid passage of faeces and air from the proximal bowel. Sometimes the bowel adjacent to the stent collapses completely, giving the impression of inadequate stent position or a further stenosis; this can be disconcerting for a less-experienced operator, but comparison with the preinsertion images should confirm correct position and avoid unnecessary placement of an additional stent.

4 Discussion

The results of published series and trials of colonic stenting are varied, and some studies were stopped because of unacceptably high complication rates in the stented group (van Hooft et al. 2014; Sagar 2016; Borowiec et al. 2016). The reported initial technical success of stenting varies from 83 to 100%, with a clinical success of 77–98% (van Hooft et al. 2014).

4.1 Stenting Versus Surgery

Many of the published studies concentrate on comparing the outcome of stenting versus surgical approaches.

A meta-analysis performed from a surgical perspective (De Simone et al. 2017), considering stenting versus surgery either as bridge to surgery or as a palliative procedure found no statistically significant differences in morbidity (stent 37.36%, surgery 50.07%), mortality (stent 8.2%, surgery 7.82%), or length of survival. In addition, stenting was associated with a statistically significant higher local recurrence rate at 1 year when compared with emergency surgery (36.7% vs 18.6%), and there is debate whether the mechanical properties of the stent and insertion techniques are directly responsible for tumour seeding. Perforation associated with stents is correlated with a particularly high (83%) rate of recurrence (van Hooft et al. 2014). Nevertheless, there was no difference in overall survival (De Simone et al. 2017).

The 2014 clinical guidelines of the European Society for Gastrointestinal Endoscopy (ESGE), issued after reviewing essentially the same data, reach similar conclusions, but with a slightly different emphasis (van Hooft et al. 2014). They quote trials showing technical success of stent insertion as 88–100%, with clinical relief of obstruction in 93%. This compares with clinical relief of obstruction from acute surgery in 100%. The stented patients have a lower 30-day mortality (4% versus 11%), but this is statistically significant in only one meta-analysis. Other statistically significant advantages of stenting include a shorter length of hospital in patient stay (10 day versus 19 day), and of intensive care admission rate (0.8 vs 18%). Short-term complications were more common in the surgical group and long-term complications in the stented group. Their recommendations include the statement that "(stent) placement is the preferred palliation for malignant colonic obstruction".

One advantage that stenting has over surgery is the reduced financial cost. The figures will vary between health systems but estimates of savings vary from 50 to 20%, depending on subsequent surgical procedures (de Gregorio et al. 2004).

4.2 Choice of Endoscopic or Fluoroscopic Technique

Several studies have shown no significant difference in outcomes or complications between

endoscopic or non-endoscopic techniques. The ESGE clinical guidelines (van Hooft et al. 2014) make a "weak recommendation" for combined endoscopic and fluoroscopic placement. There is no definite evidence for superiority of the endoscopic technique, but they quote studies with a trend to higher technical success.

A population-based study of patients receiving stents in Ontario, Canada (Borowiec et al. 2016) found no difference in outcomes between endoscopically and radiologically inserted stents. Two-thirds of the stents were inserted by gastroenterologists or surgeons, one-third by radiologists. The authors comment that endoscopic placement was more likely to occur in community, radiological placement in an academic institution. Most stents were placed for palliation, but a third of the stented patients underwent a subsequent intervention. Patients whose initial stents had been placed radiologically were less likely to have subsequent surgery. The authors comment "This finding could reflect better performance of radiologically placed stents in palliative patients or could indicate a preference for endoscopically placed stents when the intention is to bridge to surgery".

A study from a single centre in Korea (Kim et al. 2013) specifically compares the outcome of the endoscopic and radiological techniques. This found that two-thirds of procedures were performed using the endoscopic method, which had a higher technical success rate (100%) than the radiological method (92%). Several of the radiological cases required endoscopic assistance. However, there were more technical problems in the endoscopic group, e.g. a second obstructing lesion was missed in one of the endoscopic cases, and the overall immediate clinical success rates were similar. During follow-up, 32% of endoscopically placed stents and 15% of radiologically placed stents developed complications, but the difference was not statistically significant. The median stent patency was 70 days in the endoscopic group and 93 days in the radiological group, but again the difference was not statistically significant.

De Gregorio et al. (de Gregorio et al. 2004) comment that avoiding the use of endoscopy reduces costs and avoids the need for sedation, but they concede that use of endoscopy reduces radiation dose. Kim et al. (2013) describe similar advantages for the radiological technique, but prefer the endoscopic approach because of the ease of access to the tumour and the ability to place stents through the working channel of the endoscope.

The success of stenting by either technique seems to depend on operator experience (De Simone et al. 2017); minimum experience of 10 or 20 cases has been suggested for proficiency (van Hooft et al. 2014; Sagar 2016).

4.3 Choice of Stent Design

There is a choice of stents on the market. The major distinction is between covered and uncovered stents. Covered stents are more resistant to subsequent tumour ingrowth, but are also more likely to migrate out of position (Sagar 2016; de Gregorio et al. 2004). As the median survival time in irresectable (stage IV) cancer is 4–17 months, migration may well be a more significant disadvantage than ingrowth. In a series of patients from the Mayo Clinic luminal patency was maintained until death in 85% of stented cases, a median stent patency of 90 days (Small et al. 2010). The Canadian group report median survival of 199 days (Borowiec et al. 2016). However, the review of the literature in the ESGE guidelines includes papers reporting patencies of up to 343 days, and the guidelines allow use of either pattern of stent (van Hooft et al. 2014).

4.4 Use of Stenting as a Bridge to Surgery

Stenting has long been proposed as a method of initial decompression of acute large bowel obstruction with the aim of reducing the need for initial colostomy and enabling surgical excision of the tumour as a single-step procedure. The weight of evidence and published guidelines now discourage the use of stenting in this context because many studies indicate a greater local recurrence rate in patients with stents. The current consensus is that stents should only be used

for this purpose in patent with multiple comorbidities which pose a high anaesthetic risk (van Hooft et al. 2014; Sagar 2016).

4.5 Author's Own Results and an Interesting Complication

The results of stenting at the author's institution have not been published, but a local audit in 2011 compared the results of radiologically and endoscopically placed stents (Mozdiak et al. 2011). Technical success was similar in each group (endoscopic 79%, radiological 83%), and perforation rates were 5% for endoscopic and 3% for radiological approaches. A 30-day survival was better for endoscopy (82% versus 73%), but at 90 days there was more balance (64% versus 61%). None of these differences was statistically significant, but there was a significantly lower rate of stoma insertions in the radiological group (19% endoscopic, 3% radiological). These results are consonant with the published literature.

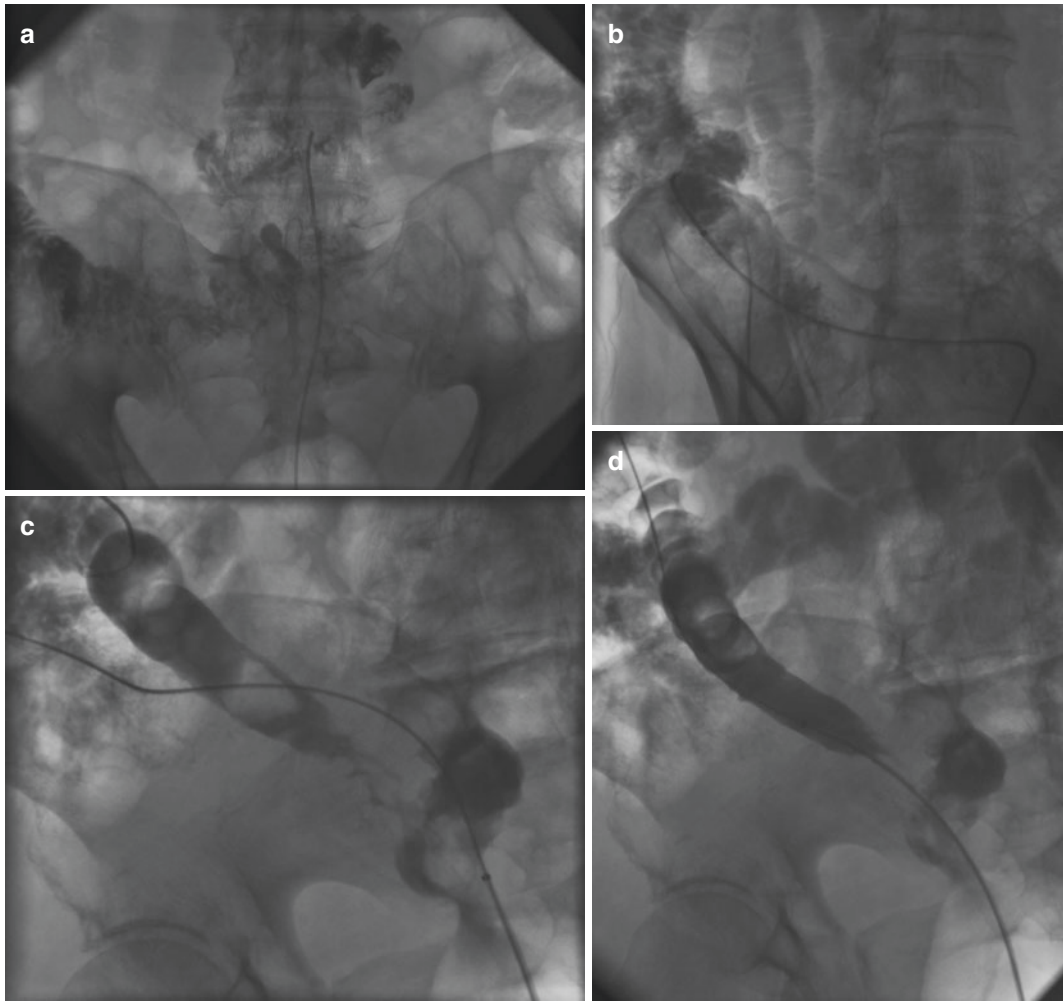

Fig. 2 Insertion of a stent in a case of tumour in the distal sigmoid with multiple fistulae to small bowel. (**a**) The position of the catheter is unusual; injection of a small amount of contrast reveals the tip lies in a small bowel loop rather than a perforation. (**b**) The position of the catheter now appears to be correct, but contrast injection again reveals a small bowel loop. (**c**) The sheath has been partially withdrawn leaving the catheter *in situ*, and contrast injection now demonstrates the correct path through the tumour and the sigmoid proximal to it. (**d**) The tumour has been crossed and the guidewire now lies in the sigmoid. (**e**) A stent has been correctly inserted in the colon

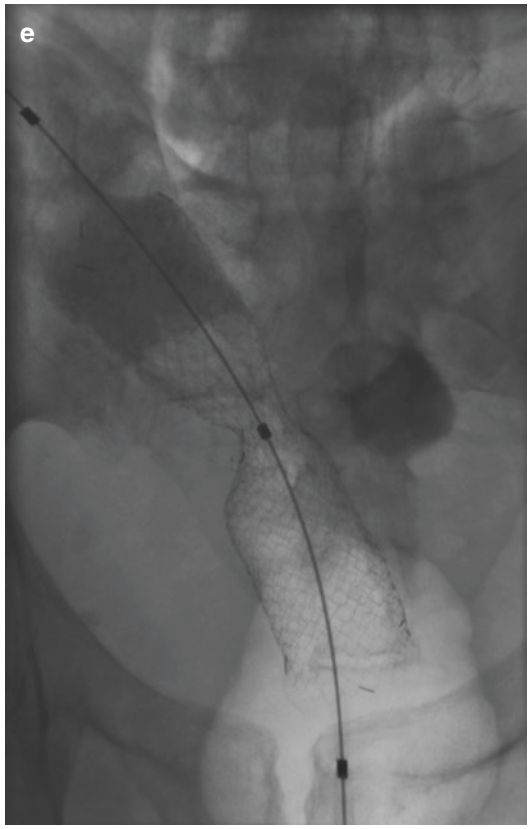

Fig. 2 (continued)

A complication which has occurred, not described in the literature as far as I am aware, is placement of a stent through a fistula into the small bowel. On the first occasion, the error was not recognised until the surgeon performed colonoscopy to investigate the lack of clinical improvement. A few months later, during another case, the catheter was seen to pass into an unusual location, and was found to be in small bowel (Fig. 2a). The catheter was eventually manipulated into the proximal large bowel, and a stent inserted in a satisfactory position (Fig. 2f). The patient lived for 4 months without further intervention. No further similar cases have been encountered in the intervening 12 years.

5 Conclusion

Insertion of an expanding metal stent is an option for patients with left colonic obstruction due to malignancy, particularly suited to cases where palliative rather than curative treatment is contemplated. Arguably stenting should be avoided in patients for whom curative surgery is possible (De Simone et al. 2017). The advantages of stenting over surgery in terms of morbidity and mortality are not as great as interventionists and endoscopists may have hoped, but there is a trend to lower morbidity, and considerable savings in resources. This relatively marginal benefit may explain why stenting is not used more widely; in the Canadian study only 5% of patients with malignant obstruction had a stent inserted (Borowiec et al. 2016). An endoscopic, fluoroscopic, or combined approach may be used, with a small advantage for endoscopy in terms of initial technical success in crossing the lesion which is not carried forward into clinical outcomes, where there is balance, and possibly marginal advantage to the radiological approach. There is a much greater variation in outcomes amongst published studies, certainly reflecting levels of operator experience, and possibly variant patterns of referral of patients at different stages of disease progression.

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Part VII

Drainages

Effusions

Chantal Z. J. Liu and Raymond J. H. Chung

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Abstract

Effusions are common in palliative care patients, with malignant pleural effusions being associated with advanced disease and a poor prognosis. Interventional radiology can greatly benefit these patients by relieving dyspnoea and minimising the need for subsequent invasive procedures. This chapter discusses various techniques, including pleurodesis and indwelling pleural catheters, which are long-term solutions to pleural effusions.

C. Z. J. Liu (✉)
St George's Hospital Medical School, London, UK
e-mail: chantal.liu@doctors.org.uk

R. J. H. Chung
Department of Diagnostic Radiology, Khoo Teck Puat Hospital, Singapore, Singapore
e-mail: rchung@doctors.org.uk

Abbreviations

ARDS	Acute respiratory distress syndrome
BTS	British Thoracic Society

© Springer Nature Switzerland AG 2021

P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_26

CT	Computed tomography
EORTC	European Organisation for Research and Treatment of Cancer Quality of Life
IPC	Indwelling pleural catheters
MPE	Malignant pleural effusions
MRI	Magnetic resonance imaging
PET-FDG	Positron emission tomography with fluorine 18-labelled fluorodeoxyglucose
SIR	Society of Interventional Radiology

1 Introduction

Pleural effusions are common in palliative care patients, with about half of those with newly diagnosed cancer being malignant. Malignant pleural effusions (MPE) refer to the presence of malignant cells in pleural fluid and is associated with disseminated or advanced disease with a poor prognosis. Whilst any malignant cell type can result in MPE, most are secondary to primary tumours of the lung, breast and ovary, or lymphomas (Heffner and Klein 2008; Roberts et al. 2010). The median survival of these patients is 3–12 months, and prognosis can be predicted using the LENT score which stratifies based on pleural fluid LDH, ECOG score, serum neutrophil-to-lymphocyte ratio, and tumour type (Roberts et al. 2010; Clive et al. 2014). A subgroup of pleural effusions in this patient population may be seen as part of a paraneoplastic process, such as pulmonary embolism, thoracic duct obstruction, superior vena cava compression, and obstructive pneumonia, in which there is a better prognosis than MPE (Ferreiro et al. 2017).

Patients with MPE are typically dyspnoeic and may have constitutional symptoms, such as weight loss and malaise. Management is dependent on the patient's symptoms and overall condition, including primary tumour type, pulmonary elastance, and patient preference (Roberts et al. 2010). Drainage of an effusion can relieve dyspnoea, and with the appropriate therapeutic intervention, minimise subsequent invasive procedures and hospital stay for palliative patients (Lorenzo et al. 2014).

In this chapter, we will discuss the available interventional procedures for the management of effusions in palliative care, including thoracentesis, pleurodesis, indwelling pleural catheters (IPC), and pleuroperitoneal shunts.

2 Indications

Drainage of effusions typically depends on a patient's symptoms, with those experiencing distressing dyspnoea being candidates for therapeutic thoracentesis and chest drain insertion. For those with sufficient symptomatic improvement, long-term solutions such as an IPC can be placed to avoid repeated thoracenteses. The British Thoracic Society (BTS) offers a management algorithm for MPE (Fig. 1). In asymptomatic patients, drainage is not necessarily required, unless needed for diagnostic purposes and in guiding treatment decisions (Feller-Kopman et al. 2018).

3 Imaging

Imaging the effusion prior to intervention is beneficial in allowing assessment of its volume, identification of features more suggestive of an MPE (compared to a simple/reactive effusion), and in guiding interventional procedures. Free pleural fluid tends to collect in the posterior costophrenic recess, with ~50 mL of fluid causing blunting of the region on a lateral chest radiograph. Those with a large pleural effusion have a higher likelihood of having a malignant aetiology. These usually have a characteristic meniscus sign, which results from a large volume of fluid tracking superiorly along the pleural surface after filling the costophrenic recess, hemithorax

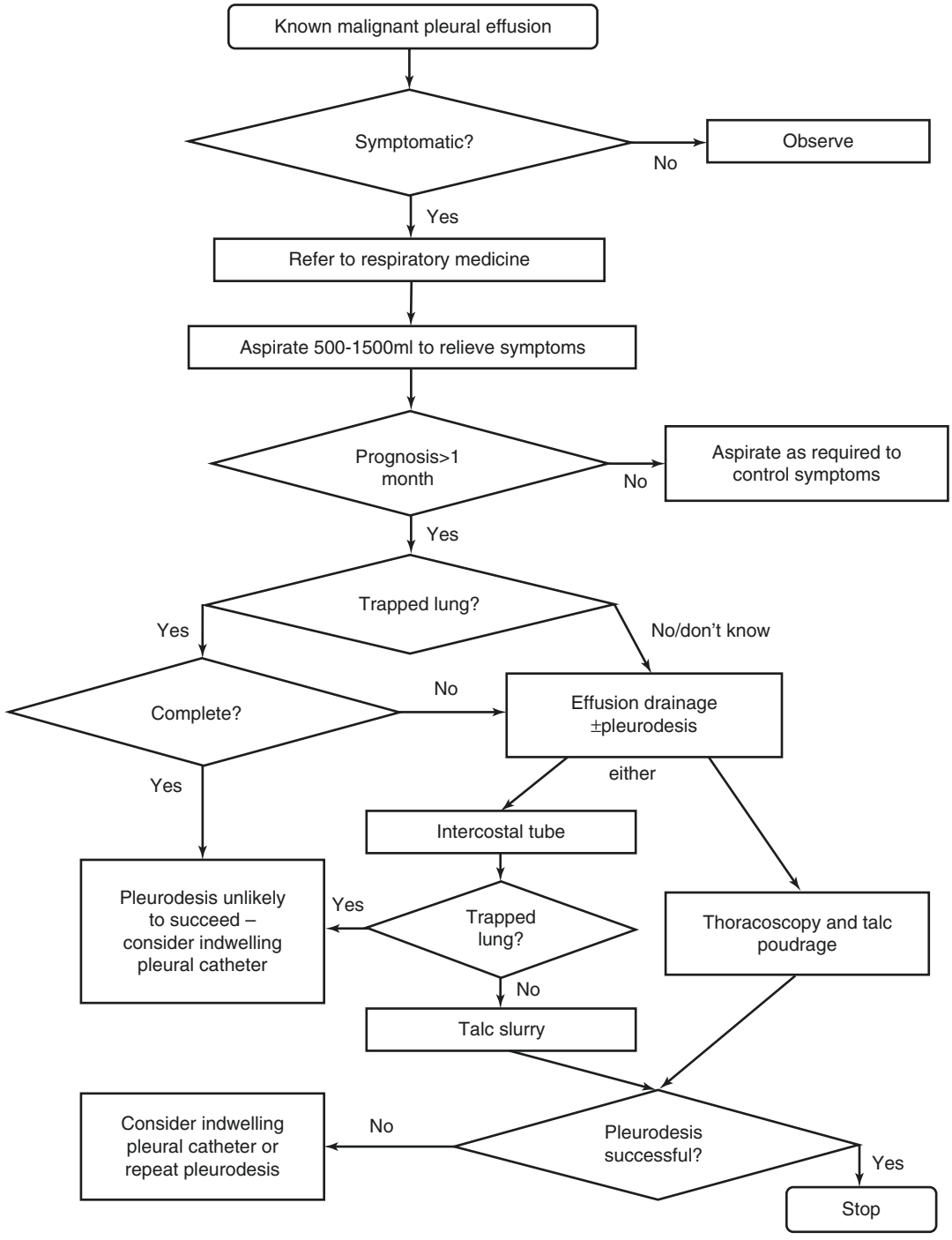

Fig. 1 BTS management algorithm of MPE (Roberts et al. 2010)

opacification, mediastinal shift, and occasionally an inverted diaphragm (Qureshi and Gleeson 2006).

Ultrasound is useful for visualising small effusions (~5 mL) and has a 94% sensitivity and 98% specificity when detecting pleural effusions (Yousefifard et al. 2016). It is the most common imaging modality used to guide interventional procedures and is useful for identifying suitable sites for thoracentesis and chest drain insertion. Features of MPE on ultrasound include hypoechoic pleural thickening with irregular/unclear borders in cases of malignant mesotheliomas, and multiple hypo to moderately echogenic regions in cases of metastatic tumours (Mayo and Doelken 2006). An echogenic swirling pattern, where numerous echogenic floating particles are observed within the pleural effusion, is also correlated with MPE (Chian et al. 2004).

CT is the most useful modality for evaluating suspected MPE, which is more likely when the features of circumferential or nodular pleural thickening, parietal pleural thickening >1 cm, and/or mediastinal pleural involvement are present (Qureshi and Gleeson 2006). Its use before thoracentesis has been shown to improve diagnostic sensitivity, as both visceral and parietal pleurae can be visualised (Leung et al. 1990; Yilmaz et al. 2005). CT is also helpful for detecting the aetiology of paraneoplastic pleural effusions by revealing tumour involvement of thoracic structures (e.g. superior vena cava) (Heffner and Klein 2008). Current BTS guidelines recommend that CT be performed if pleural effusion analysis is unable to ascertain the aetiology of the pleural exudate (Du Rand and Maskell 2010).

Triple-pulse sequence MRIs are highly sensitive for small effusions. They tend to be reserved for complex cases and are useful for differentiating exudates from transudates. PET-FDG is used to rule out MPE when cytology is negative, and combined FDG PET/CT can be used to improve localisation for guided biopsy (Heffner and Klein 2008).

4 Contraindications

There are few contraindications to draining effusions, however, the risks and benefits of drainage should be weighed for each individual patient together with the clinical team. Safe access from skin entry site to effusion is an important consideration, as well as the coagulation profile of a patient (Lewandowski et al. 2013). A specific assessment of the bleeding risk and considerations of blood products and haemostatic agents should be carried out, taking into consideration the procedure being performed, and the individual patient's comorbidities.

Thoracentesis and insertion of an IPC are generally considered low-risk procedures. Society of Interventional Radiology (SIR) guidelines recommend pre-procedure laboratory tests of activated partial thromboplastin time (APTT) for those receiving unfractionated heparin and international normalised ratio (INR) for those on warfarin or with suspected/known liver disease, with INR >2.0 being the treatment threshold (i.e. fresh frozen plasma, Vitamin K). Transfusion is recommended for patients with a platelet count <50,000/μL. Prior to the procedure, clopidogrel should be withheld for 5 days and one administration of therapeutic dose low molecular weight heparin (LMWH) should be omitted. Aspirin may be continued as usual (Patel et al. 2012).

5 Techniques

5.1 Thoracentesis

Thoracentesis is a common diagnostic and/or therapeutic procedure involving the aspiration of pleural fluid. For diagnostic purposes, up to 60 mL is required to be sent for cytology, immunohistochemistry and, in suspected lymphomas, flow cytometry (Ferreiro et al. 2017; Swiderek et al. 2010). For therapeutic procedures, a maximum of 1.5 L should be drained on a single occa-

Table 1 Technique of chest drain insertion

• Review imaging to identify safest, and ideally shortest, route to the collection which will allow maximal drainage—normally with drainage catheter in the most dependent position of the collection
• Position patient and confirm route, normally by ultrasound or CT guidance
• Prepare skin and drape using sterile technique
• Administer local anaesthetic and consider intravenous sedation
• Create small incision with a scalpel and perform blunt dissection of underlying soft tissue to allow easier traversal of catheter
• Employ either the Seldinger or Trocar technique, usually dependent upon operator preference
• Seldinger technique:
– Obtain initial needle access under imaging guidance (normally ultrasound)
– Aspirate fluid after imaging confirmation that needle is within the cavity
– Insert guidewire through the needle into the cavity
– Remove needle and perform serial tract dilatation to accommodate a suitable sized catheter
– Remove guidewire
• Trocar technique:
– Advance catheter containing a hollow metal stiffener and inner sharp stylet directly into the fluid collection under imaging guidance
– On imaging confirmation of catheter tip within the collection, advance catheter over the metal stiffener and trocar needle into the cavity
– Aspirate to confirm catheter position
– Acquire samples for testing
• Secure catheter, acquire samples for testing, and attach to a suitable (underwater seal) drainage system (Lewandowski et al. 2013)

sion although this depends on each patient's symptoms (Roberts et al. 2010).

Ultrasound guidance is recommended to increase the success rate of thoracentesis, by aiding the identification of a suitable entry site, avoidance of solid organ injury, and by reducing the risk of pneumothorax.

In palliative care patients with a short life expectancy (<1 month), or those who respond quickly to systemic therapy, thoracentesis is a suitable method of effusion drainage (Roberts et al. 2010; Stokes 2007). However, there is a high recurrence rate, with 32% needing a second pleural procedure within 14 days and 23% requiring one after 14 days (Ost et al. 2018). Whilst repeated thoracenteses can be performed when required, each procedure increases the risk of pleural adhesions, potentially making future drainage more complicated. Furthermore, the risk of bleeding, infection, fluid loculation, and re-expansion pulmonary oedema also increases (Stokes 2007).

In those with a large effusion, a temporary chest drain insertion allows for controlled drainage over several days before removal. The technique of drain insertion is similar to that of any image-guided drain procedure (Table 1).

5.2 Pleurodesis

Pleurodesis is the induction of pleural fibrosis to obliterate the pleural space with the aim of preventing subsequent accumulation of pleural fluid. This is achieved by introducing a sclerosing agent such as talc, tetracycline, or bleomycin into the pleural space after drainage of the pleural fluid, to cause chemical or mechanical pleural irritation (Ferreiro et al. 2017; Stokes 2007).

The sclerosing agent can be introduced either in the outpatient setting through a chest tube or

via video-assisted thoracoscopic surgery, which requires hospitalisation and general anaesthetic. According to the BTS, both methods have similar efficacies. Talc is a commonly used sclerosant and is preferred over the others due to its efficacy and equivalent toxicity (Shaw and Agarwal 2004). Large-particle talc (>15 microns) is preferred, so as to reduce the risk of ARDS abbreviation used in Complications section later on. Pleurodesis is not suitable for patients with a trapped lung (i.e. non-expandable after fluid drainage) (Maskell et al. 2004).

Following insertion of a chest drain for an MPE, a chest radiograph is performed to confirm lung re-expansion and position of the tube when drainage decreases to <100–200 mL over 24 h. Lidocaine (3 mg/kg, max. 250 mg) is instilled into the pleural space, followed by 4–5 g of sterile graded talc in 50 mL of 0.9% saline. The tube is clamped for 1–2 h and returned to drainage afterwards. When drainage output is <100–200 mL, typically 24–48 h post-administration of sclerosant, the intercostal tube is removed (Roberts et al. 2010). There is currently no evidence that rotating the patient after administering sclerosing agent improves success of the procedure (Ferreiro et al. 2017).

Most patients experience symptomatic improvement, and success is normally determined by the lack of re-accumulation of pleural fluid within 30 days. Common side effects include chest pain and fever (Ferreiro et al. 2017; Stokes 2007).

5.3 Indwelling Pleural Catheters

Indwelling Pleural Catheters (IPC) are subcutaneously secured silicon tubes that end in a one-way valve. They are inserted to allow continuous drainage of pleural effusions so as to maintain lung expansion (Ferreiro et al. 2017). Their use in managing MPE has increased over the past decade, as they offer a long-term management solution in palliative patients (McCracken et al. 2018). IPC can be performed in patients who have a good systemic response to thoracentesis, a reasonable life expectancy and ideally a reliable caregiver, since the catheters allow patients to drain any recurrent fluid at home (Stokes 2007).

Insertion of an IPC can be done in the outpatient setting and is suitable for patients who are unable to have pleurodesis (e.g. due to trapped lung) or in cases of failed pleurodesis. There is a high rate of technical success, with reports of 85% not requiring catheter intervention or separate therapeutic paracentesis within 12 weeks or until death (Courtney et al. 2008). Complication rates are low (13%) and include pleural infection, cellulitis, tumour seeding of the catheter track, and catheter obstruction (Putnam Jr et al. 1999). Another benefit is spontaneous pleurodesis, which has been reported in 51% of patients following IPC insertion (Davies et al. 2012).

PleurX (Denver Biomaterials, Golden, CO, USA) is a commonly used IPC that was approved by the US Food and Drug Administration in 1997 for use in patients with MPE. It is a 15.5F, 66 cm long silicon catheter with side holes along the distal 24 cm. The catheter is flexible and soft to increase patient comfort and has a single polyester cuff to reduce the risk of catheter migration. It also contains a valve that prevents leakage from the catheter, as well as preventing air entry into the pleural space (Fig. 2) (Stokes 2007). Table 2 outlines the technique used to insert a PleurX drain, and Fig. 3 shows various imaging of an inserted PleurX catheter.

According to a multicentre observational study assessing quality of life in patients who had an IPC inserted for MPE, the procedure significantly improves patient symptoms. Patients self-reported using the EORTC QLQ-C30 questionnaire, which is a widely used 30-item cancer-specific questionnaire addressing quality-of-life domains using global, functional, and symptoms scales. Lung cancer patients also filled in the QLQ-LC13, which is a supplementary component assessing additional parameters such as dyspnoea. There was a significant decrease of 9.59 (scale of 0–100, with higher scores corresponding to higher levels of symptomatology) in

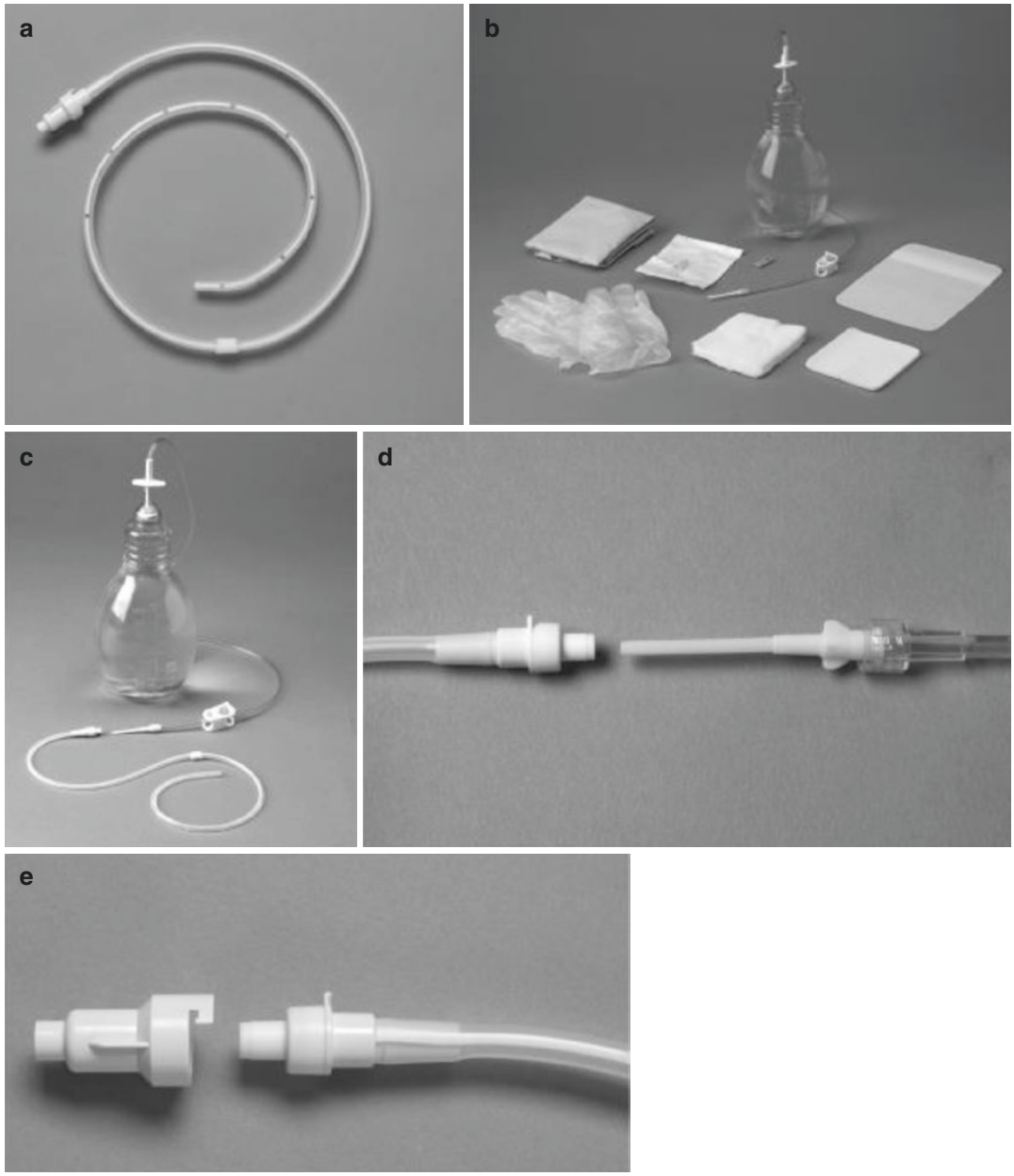

Fig. 2 (**a**) PleurX catheter (**b**) Sterile supply kit provided for drainage (**c**, **d**) Connector at the end of drainage bottle fits inside the catheter, opening the one-way valve in the hub of the PleurX (**e**) PleurX cap for when it is not in use (Stokes 2007)

the mean score for the symptoms scale 30 days post-IPC insertion. In lung cancer patients, a significant decrease of 21.62 (scale of 0–100) was reported for dyspnoea 30 days post-IPC insertion compared to before the procedure (Lorenzo et al. 2014).

Table 2 PleurX drain insertion technique

• Prepare skin and drape for aseptic technique
• Administer local anaesthesia at access site
• Under ultrasound guidance, puncture a suitable access site with a guide needle into the pleural space. This is typically via a low intercostal space such that the catheter can eventually lie across the posterior costophrenic sulcus
• Advance a 0.035 stiff guidewire through the needle, and serially dilate the entry site before inserting a 16F tapered peel-away sheath
• Administer local anaesthesia along the proposed subcutaneous tunnel, which is directed anteriorly, to allow easy access to the catheter for the patient. Care should also be taken to ensure that the exit site is not placed where the patient's waistband would typically lie
• Place the PleurX catheter through the tunnel in an antegrade manner
• Minimise air entry into the pleural space when advancing the catheter by placing a dilation catheter (e.g. 6.3F van Andel, Cook, Bloomington, IN) through the most proximal side hole and out the distal end of the PleurX to temporarily occlude the side holes. When removing the dilator from the peel-away sheath, pinch the sheath to reduce air entry into the chest
• Advance the PleurX catheter through the peel-away sheath and remove the wire, dilator, and peel-away sheath
• Close the site and secure the PleurX at the exit site with a non-absorbable suture (Lorenzo et al. 2014; Stokes 2007)

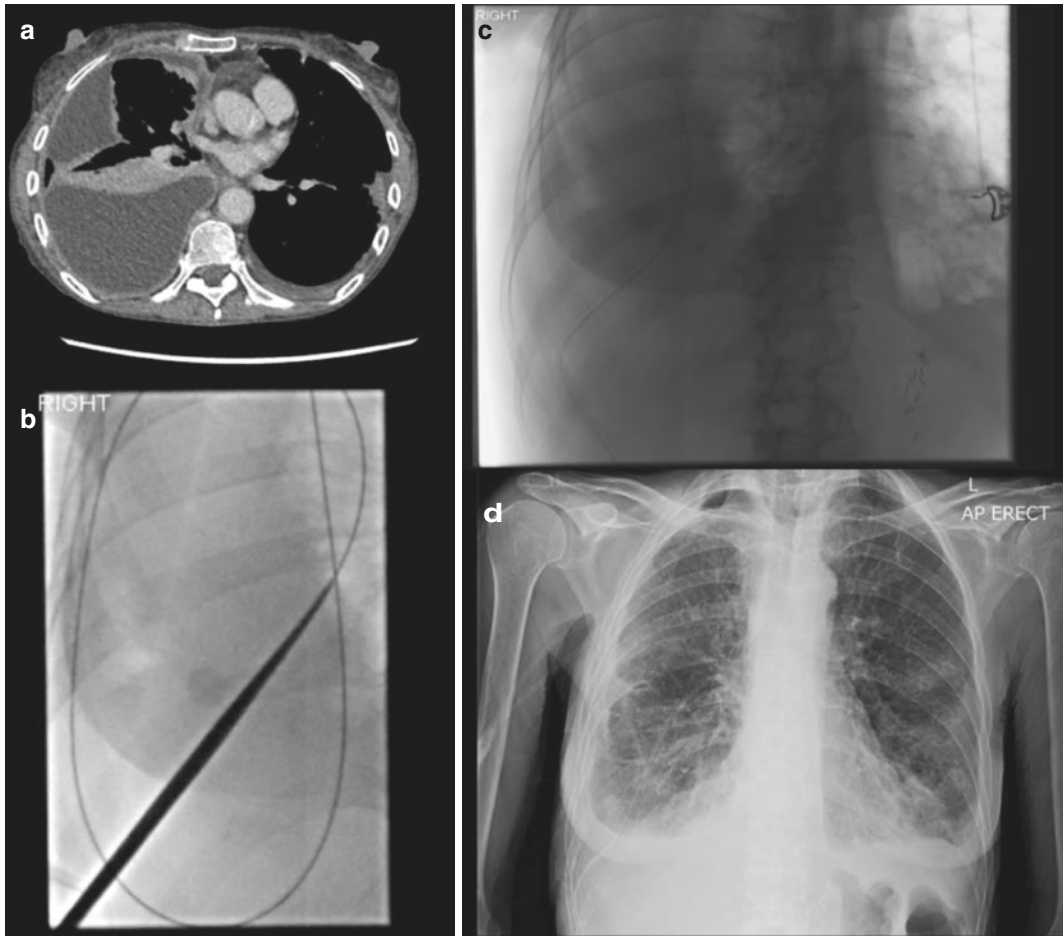

Fig. 3 (**a**) Axial contrast-enhanced CT illustrating large right pleural effusion pre-procedure. (**b**) Intra-procedural fluoroscopic image of looped guidewire and dilator into right pleural cavity. (**c**) Post-procedure radiograph with PleurX drain in situ. (**d**) Follow up chest radiograph with PleurX drain in situ and significant interval resolution of the pleural effusion

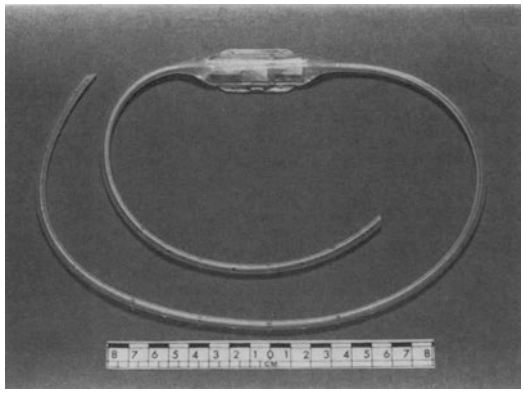

Fig. 4 Denver pleuroperitoneal shunt (Tsang et al. 1990)

5.4 Pleuroperitoneal Shunts

Pleuroperitoneal shunts are an alternative method of managing recurrent pleural effusions in palliative care patients. They allow pleural fluid to be continuously shunted into the peritoneal cavity and can be useful in cases when pleurodesis is contraindicated. Effective use of pleuroperitoneal shunts for palliative care were first reported in 1982 and have since been used to control benign and malignant pleural effusions as well as paraneoplastic chylous effusions (Heffner and Klein 2008; Tsang et al. 1990).

A Denver (Denver Biomaterials, Golden, CO, USA) pleuroperitoneal shunt can be inserted for this function and contains two unidirectional valves which open at positive pressures (~1 cm H_2O) (Fig. 4). During expiration, normal intrapleural pressure reaches ≥4 cm H_2O. As such, this allows pleural fluid to spontaneously flow from the pleural cavity into the peritoneal cavity with each breath. In patients with a pleural effusion, the greater pressure difference between the pleural space and intra-abdominal cavity allow for larger amounts of fluid to be shunted into the peritoneal space. When this pressure gradient is low, a compressing pump chamber is used to induce flow and helps to maintain shunt patency (Tsang et al. 1990).

Shunt insertion is typically performed under general anaesthetic although this can be done under local anaesthesia as well. After draining the pleural fluid via thoracoscopy or short thoracotomy, the pleuroperitoneal shunt is inserted. A 2–3 cm transverse incision is made in the hypochondrium to expose the peritoneal cavity, and the pleuroperitoneal shunt is tunnelled from the chest to the abdomen, with a shunt pumping catheter lodged in the subcutaneous pocket that overlies the costal margin. This pump is then compressed regularly for the first 24 h post-procedure to minimise the risk of shunt occlusion (Tsang et al. 1990).

Reported complications of pleuroperitoneal shunts include shunt occlusion by blood clots or infected fibrin debris, and peritoneal dissemination of tumour cells causing malignant ascites. Whilst studies have shown that pleuroperitoneal shunts can benefit patients with MPE by providing symptomatic relief, it is not as common a procedure due to the high incidence (~25%) of shunt occlusion. Furthermore, the requirement of pumping the shunt frequently during the day can be difficult for patients and/or their carers (Tsang et al. 1990; Feller-Kopman et al. 2007).

The median duration of shunt function is reported as ~9 months, with a maximum duration of 23 months. Most patients benefit from its palliative effect of symptomatic relief and die of their underlying malignancy without requiring further admission for repeated drainage after having the shunt inserted (Tsang et al. 1990). Nonetheless, the risks and benefits should be weighed together with the patient and the multidisciplinary team before proceeding with this technique.

6 Complications

Complications of draining pleural effusions can be the result of various factors and depends on the technique used as well as an individual patient's condition. A common complication is pneumothorax, which has a reported incidence of 1.5% for thoracentesis and 1.3% for IPC insertion (Ost et al. 2018). This risk can be minimised by using ultrasound guidance which is thus recommended to guide needle insertion regardless

of which technique is employed to drain the effusion (Barnes et al. 2005).

Another complication that can arise is re-expansion pulmonary oedema, which is reportedly more likely to occur when draining a large volume of pleural fluid at one time and/or using early and excessive pleural suction. The pathophysiology is attributed to reperfusion injury of the underlying hypoxic lung, increased capillary permeability and local production of neutrophil chemotactic factors. Whilst re-expansion pulmonary oedema is rare and there have also been reports of it being independent of the volume of fluid reported independent of the volume of fluid removed (Feller-Kopman et al. 2007), the BTS guidelines recommend a conservative approach, advising large pleural effusions to be drained incrementally, with a maximum of 1.5 L being drained on the first occasion. Subsequent drainage should be capped at 1.5 L with 2-h intervals and stopped if the patient experiences chest discomfort, persistent cough, or vasovagal symptoms (Roberts et al. 2010).

Acute respiratory distress syndrome (ARDS) is a rare but serious complication of pleurodesis. Non-graded talc increases the risk of arterial hypoxaemia and acute pneumonitis, leading to acute respiratory failure both via atomiser (talc poudrage) and suspension (talc slurry). Thus, graded talc (with particle size >15microns) is recommended in doses of <5 g (Roberts et al. 2010; Fortin and Tremblay 2015). A prospective cohort study of 558 patients with MPE underwent thoracoscopy and talc poudrage with 4 g of calibrated French large-particle talc and found that no patients developed ARDS, suggesting that large-particle talc is safe for pleurodesis use (Janssen et al. 2007).

Pain is another common complication that warrants consideration for palliative patients undergoing pleural effusion drainage. A Cochrane meta-analysis reported that 31% of patients who underwent talc pleurodesis experienced pain, however in a multi-institutional study of the effectiveness and safety of IPC insertion for MPE, only 4.7% of the patients who had an IPC inserted experienced severe pain requiring patient-controlled analgesia (Shaw and Agarwal 2004; Putnam Jr et al. 1999).

7 Follow-Up

After draining a pleural effusion, the patient should be closely monitored, and any complications should be managed before discharge. In IPC insertion, patients and their carers are taught how to manage the catheter and vacuum bottles at home and are provided with written instructions as well as emergency contact numbers. In particular, they should be instructed to slow down or terminate fluid drainage should the patient feel short of breath, experience chest pain or tightness, and/or develop a persistent cough (Lorenzo et al. 2014; Wahidi et al. 2017).

The ASAP trial, a randomised study comparing aggressive daily drainage to standard alternate day drainage, reported a higher rate of autopleurodesis in patients who underwent daily drainage (47% vs 24%). The study also demonstrated a shorter time to freedom from catheter with daily drainage (Wahidi et al. 2017).

Although greater responsibility is shifted to the patient and their carers by inserting an IPC for long-term management, the ASAP trial reported high levels of satisfaction experienced by the patient/carers with managing catheters in the home setting (Wahidi et al. 2017). This suggested the value of maintained autonomy experienced by terminally ill patients in managing their IPC.

8 Comparison of Techniques

Therapeutic drainage prior to more definitive management helps confirm if fluid drainage will improve a patient's symptoms as well as identify the presence of a trapped lung. Thus, thoracentesis and/or temporary drainage catheter insertion is often performed first. More than half of MPE reaccumulate after the procedure, warranting IPC insertion and pleurodesis as long-term solutions. These definitive treatments result in fewer subsequent pleural interventions and pneumothoraces as compared to having multiple thoracenteses (Feller-Kopman et al. 2018; Ost et al. 2018).

In cases of trapped lung, failed pleurodesis or loculated effusions, the American Thoracic

Society recommends IPC insertion (Feller-Kopman et al. 2018). Aside from this, various studies have failed to consistently identify the superior technique (IPC vs pleurodesis), given the multifactorial nature of palliative outcome measures.

The AMPLE Study was a randomised clinical trial comparing the effect of IPC and talc pleurodesis with regard to hospitalisation days in patients with MPE. They found that IPC insertion is associated with significantly shorter all-cause hospital admissions than pleurodesis (10 vs 12 days), and shorter effusion-related hospital stay (1 vs 4 days). They also reported that further ipsilateral invasive pleural drainage was much lower in patients who had an IPC inserted compared to talc pleurodesis (4.1% vs 22.5%) (Thomas et al. 2017).

On the other hand, the TIME-2 Randomised Controlled Trial, which focused on comparing dyspnoea relief from IPC insertion and talc pleurodesis, reported adverse events (e.g. cellulitis and pleural infections) in IPC insertion to be higher than that of talc pleurodesis (40% vs 13%) although they found no statistical difference between the two techniques for serious adverse events (Davies et al. 2012).

Cost is another important consideration for patients and the clinical team. A cost-effectiveness analysis found that IPC insertion is cheaper than pleurodesis, when patients have a shorter life expectancy (<14 weeks). However, when nursing time for catheter drainage (2 h per week) was factored in, IPC was more expensive than pleurodesis (Olfert et al. 2017). Thus, selecting between the two also depends on local resources and individual patient preferences.

Recent studies have combined IPC and talc pleurodesis, showing that a combination of both can lead to a higher chance of pleurodesis at 35 days without deleterious effects, compared to inserting an IPC alone (43% vs 23%) (Bhatnagar et al. 2018a). Drug-eluting IPC using a silver nitrate slow-release coating are also being developed and trialled, the goal being that combining a pleurodesis agent like silver nitrate can improve effectiveness of achieving pleurodesis (Bhatnagar et al. 2018b). At the time of writing, these methods are not yet routine, but may soon become new techniques of managing pleural effusions in palliative patients.

9 Conclusion

Pleural effusions are common in palliative care and can be managed by therapeutic drainage. Thoracentesis and/or temporary chest drainage is normally performed first with subsequent pleurodesis or IPC insertion being options for definitive treatment. These interventional long-term solutions can hugely benefit a patient's quality of life, especially in improving distressing dyspnoea.

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Ascites and Fluid Collections

Chantal Z. J. Liu and Raymond J. H. Chung

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Abstract

Ascites is common in both benign and malignant conditions. In palliative patients, it is a significant contributor to pain, discomfort, and impaired mobility. Drainage of ascitic fluid can be performed through various interventional procedures such as repeated large volume paracentesis/drain insertion, indwelling peritoneal catheters, peritoneovenous shunts, and TIPSS. These palliative methods can dramatically relieve a patient's symptoms and improve quality of life. In this chapter, we will explore how these techniques are performed, when they are indicated as well as discuss their associated complications and how to mitigate them. A comparison of techniques and factors to consider when choosing a method of drainage will also be discussed.

C. Z. J. Liu (✉)
St George's Hospital Medical School, London, UK
e-mail: chantal.liu@doctors.org.uk

R. J. H. Chung
Department of Diagnostic Radiology,
Khoo Teck Puat Hospital, Singapore, Singapore
e-mail: rchung@doctors.org.uk

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_27

Abbreviations

AASLD	American Association for the Study of Liver Diseases
APTT	Activated partial thrombin time
DIC	Disseminated intravascular coagulation
EASL	European Association for the Study of the Liver
INR	International normalised ratio
LMWH	Low molecular weight heparin
NICE	National Institute for Health and Care Excellence (UK)
PTFE	Polytetrafluoroethylene
SIR	Society of Interventional Radiology
TIPSS	Transjugular intrahepatic portosystemic shunt

1 Introduction

Ascites has a wide aetiological basis in both malignant and non-malignant diseases. In malignancy, it is commonly associated with primary neoplasms of the colorectum, ovary, breast, pancreas, liver, or lymphoma. Non-malignant causes include liver cirrhosis, congestive heart failure, and nephrosis. When associated with oncological disease as malignant ascites, it is representative of peritoneal carcinomatosis and is typically a poor prognostic indicator. Median patient survival after diagnosis of malignant ascites is 5.7 months although this depends on the underlying malignancy (Ayantunde and Parsons 2007; Saif et al. 2009).

Palliative patients with ascites often experience increased abdominal pressure causing pain, dyspnoea, anorexia, limb swelling, and impaired mobility. Dietary changes like reducing sodium intake and diuretics typically have limited efficacy in such cases, and the culmination of symptoms can be very distressing and debilitating for patients. Thus, ascitic fluid drainage can dramatically improve a patient's quality of life by providing symptomatic relief (Saif et al. 2009; Adam and Adam 2004).

Various interventional procedures can be used to manage ascites. In this chapter, we will focus on procedures providing short-term relief such as paracentesis/drain insertion and those offering more prolonged symptom control such as indwelling catheters, peritoneovenous shunts and transjugular intrahepatic portosystemic shunts (TIPSS) (Stokes 2007; Stukan 2017).

2 Indications

Differentiating the underlying aetiology for ascites is pivotal in determining clinical management. In malignant ascites, conventional management is large volume paracentesis. An indwelling catheter or peritoneovenous shunt is indicated when the malignant ascites is recurrent (White and Carolan-Rees 2012; Martin-Hirsch et al. 2014).

Whilst there are various reports on paracentesis and the feasibility of indwelling catheters and shunts, there currently lacks standardised guidelines on when drainage is indicated or when to employ each technique. In practice, symptoms of abdominal pain, nausea, bloating, and dyspnoea are a good indication that the ascites should be drained (Smith and Jayson 2003; Chung and Kozuch 2008; Li et al. 2016).

In cases of liver cirrhosis, large volume paracentesis is indicated in patients with grade 3 or large ascites. Table 1 illustrates the grading and suggested treatment by the European Association for the Study of the Liver (EASL) (European Association for the Study of the Liver 2010).

TIPSS should be considered in patients with refractory ascites, who require frequent therapeutic paracentesis. It is also indicated when paracentesis is ineffective, such as when the ascites is loculated (European Association for the Study of the Liver 2010). Peritoneovenous shunts are indicated in patients with refractory ascites who are not suitable candidates for paracentesis or TIPSS (AASLD practice guideline—management of adult patients with ascites due to cirrhosis 2012).

Table 1 EASL grading and suggested treatment for ascites in liver cirrhosis (European Association for the Study of the Liver 2010)

Grade of ascites	Definition	Treatment
Grade 1	Mild ascites only detectable by ultrasound	No treatment
Grade 2	Moderate ascites evident by moderate symmetrical distension of abdomen	Restriction of sodium intake and diuretics
Grade 3	Large or gross ascites with marked abdominal distension	Large volume paracentesis followed by restriction of sodium intake and diuretics (unless patients have refractory ascites)

3 Contraindications

Similar to draining pleural effusions, there are few contraindications to draining ascites and the risks and benefits should be carefully weighed for each patient. The bleeding risk should be assessed and managed accordingly with blood products and haemostatic agents. Paracentesis and insertion of an indwelling catheter are considered low risk procedures whilst peritoneovenous shunt and TIPSS insertions are higher risk interventions.

For low risk patients, the Society of Interventional Radiology (SIR) guidelines recommend pre-procedure laboratory tests of activated partial thromboplastin time (APTT) for those receiving unfractionated heparin and international normalised ratio (INR) for those on warfarin or with suspected/known liver disease, with INR >2.0 being the treatment threshold (i.e. fresh frozen plasma, Vitamin K). Transfusion is recommended for patients with a platelet count <50,000/μL. Prior to the procedure, clopidogrel should be withheld for 5 days and one administration of therapeutic dose low molecular weight heparin (LMWH) should be omitted. Aspirin may be continued as usual.

In patients where there is a higher risk of significant bleeding, the SIR recommends that INR be corrected to <1.5, APTT be checked and stopped or reversed if >1.5× control, and platelet count and haematocrit be checked. Patients with platelets <50,000/μL should be transfused, and clopidogrel and aspirin should be withheld for 5 days pre-procedure. Fractionated heparin should be withheld for 24 h or up to 2 doses before the procedure (Patel et al. 2012).

In addition, EASL guidelines recommend against TIPSS procedures in cases of severe liver failure (serum bilirubin >5 mg/dL, INR >2 or Child-Pugh score >11, current hepatic encephalopathy ≥grade 2 or chronic hepatic encephalopathy), concomitant active infection, progressive renal failure, or severe cardiopulmonary disease (European Association for the Study of the Liver 2010).

4 Techniques

4.1 Paracentesis

Paracentesis involves draining ascitic fluid out of the body via a catheter inserted into the peritoneal cavity. It is a very common procedure and can be performed in an inpatient or outpatient setting, dependent upon the individual patient's condition. In the Interventional Radiology suite, ultrasound guidance is normally used as it enables identification of an appropriate site of access, presence of loculations, and avoidance of solid organ or bowel injury (Stokes 2007; White and Carolan-Rees 2012).

The technique of paracentesis/abdominal drain insertion is similar to that described for chest drain insertion in *Chapter "Effusions", Table 1*. In addition, administration of local anaesthesia along the peritoneal lining can be helpful in reducing pain associated with the procedure. It is important to avoid injury to the inferior epigastric artery, which runs along the lateral border of the rectus sheath (Stokes 2007).

After the procedure, the catheter is left in place until most of the ascitic fluid has been drained. This often exceeds 5 L and can reach up to 15 L over a 4 to 6-h period. There is currently

limited evidence that can reliably advise on the optimal speed of fluid withdrawal (White and Carolan-Rees 2012; Macken et al. 2018; Becker et al. 2006).

Colloid replacement therapy is recommended especially when >5 L of ascites is drained to avoid post-paracentesis circulatory dysfunction with renal impairment and electrolyte disturbance. Whilst there is debate about the choice of colloid replacement, the EASL advises albumin over artificial plasma expanders, which should be administered slowly to avoid cardiac overload (European Association for the Study of the Liver 2010). In cases of ascites due to liver cirrhosis, the American Association for the Study of Liver Diseases (AASLD) recommends administering an albumin infusion of 6–8 g per litre of fluid removed during large volume drainage although this may not be necessary for single paracenteses of <4–5 L (AASLD practice guideline—management of adult patients with ascites due to cirrhosis 2012).

As symptomatic relief is only temporary, most patients experience re-accumulation of fluid and require repeated large volume paracenteses. Frequent hospital visits can be expensive, and patients often wait until their ascites is of a large enough volume to be safely drained, thus resulting in them experiencing repeated episodes of ascites-related discomfort, affecting their quality of life (Keen et al. 2014). In malignant ascites, the mean duration of symptomatic relief post-paracentesis is 10.4 days. Nonetheless, paracentesis remains an effective technique in improving symptoms in 87% of patients (Ross et al. 1989).

4.2 Indwelling Peritoneal Catheters

Indwelling peritoneal catheters are commonly used in long-term management of ascites in palliative care. They can be tunnelled or non-tunnelled; the latter associated with a lower risk of peritonitis (Fleming et al. 2009). Some studies have suggested inserting indwelling "permanent" catheters after a patient has undergone 2–3 large volume paracenteses (Tapping et al. 2012; Rosenberg et al. 2004). However, the United Kingdom's National Institute for Health and Care Excellence (NICE) recognises the uncertainty of the appropriate timing for adoption of a "permanent" system (PleurX) over standard paracenteses procedures, and therefore recommend the decision to be shared between the clinician and patient (White and Carolan-Rees 2012). Examples of such indwelling peritoneal catheter systems include the PleurX peritoneal catheter and Tenckhoff catheter (Fleming et al. 2009; Ha et al. 2017).

The PleurX peritoneal catheter drainage system is commonly used and was cleared for use in the abdomen by the US Food and Drug Administration in 2005. It comprises of a 71 cm, 15.5F silicon catheter and is similar to the PleurX described under *Indwelling Pleural Catheters* in *Chapter "Effusions"*. It is inserted in a similar manner but into the peritoneal cavity (White and Carolan-Rees 2012). The access site is typically chosen such that the catheter courses inferomedially into the lower abdomen and pelvis, with the entry site often being placed above the umbilicus to prevent leakage along the tract (Stokes 2007). As with insertion into a pleural effusion, it is typically performed under ultrasound guidance (Fleming et al. 2009). Figure 1 illustrates an inserted PleurX on imaging.

Reported technical success is as high as 100% with no immediate complications at the time of the procedure, and the median duration of indwelling catheters *in situ* from placement till death is 18.5 days in malignant ascites and 85 days in non-malignant ascites (Knight et al. 2018). Several studies have shown that over 80% of peritoneal catheters remain functioning until patient death, and that they result in lower rates of re-intervention and hospital re-admission (Tapping et al. 2012; Knight et al. 2018). Furthermore, the use of tunnelled peritoneal catheters as a mode of intraperitoneal chemotherapy delivery has also been supported by a study assessing their safety and feasibility in palliative patients with malignant ascites (Ha et al. 2017).

Overall, indwelling peritoneal catheters are a safe, convenient, and more comfortable method

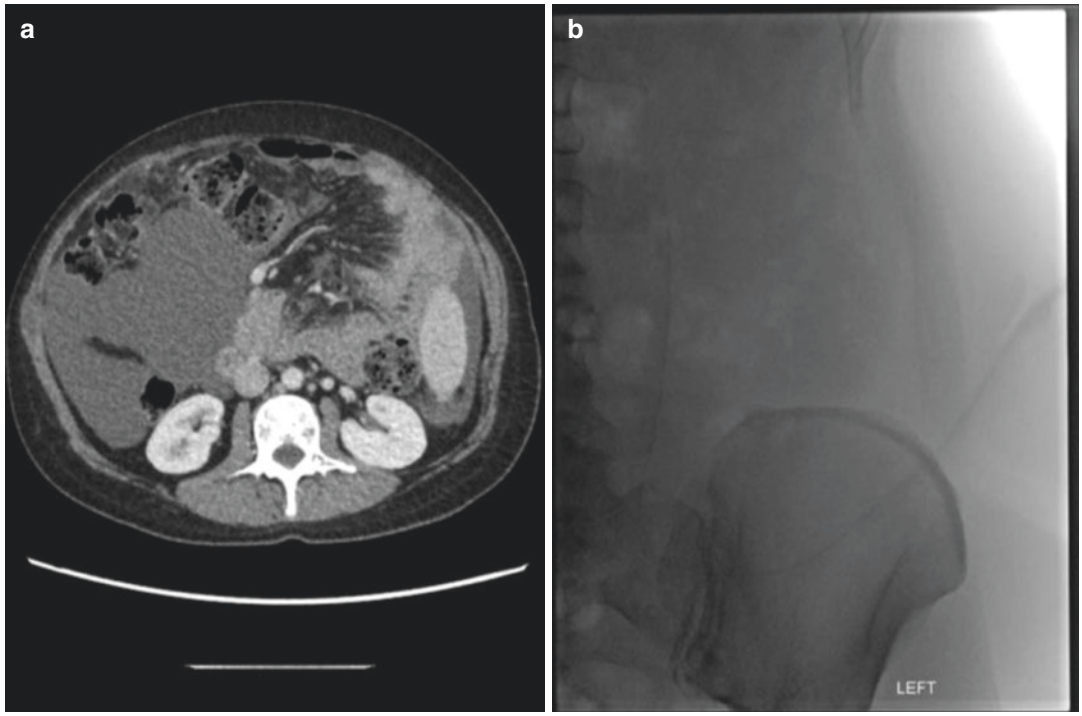

Fig. 1 (**a**) Axial contrast-enhanced CT of the abdomen depicting moderate volume ascites. (**b**) Post-procedure radiograph illustrating the inserted abdominal PleurX catheter in the left side of the abdomen

of symptom relief. It affords palliative patients with recurrent refractory ascites freedom from repeated hospital admissions for paracentesis and greater autonomy towards their end of life (Li et al. 2016; Wong et al. 2015).

4.3 Peritoneovenous Shunts

Peritoneovenous shunts were first introduced in 1974 as a method of recirculating ascitic fluid from the peritoneal cavity back into the central venous circulation. The most common currently used device is the Denver Shunt (CareFusion Corporation, San Diego, CA), which has been modified from ventriculoperitoneal shunts used for the treatment of hydrocephalus. It is used to treat malignant and non-malignant refractory ascites and can be considered in patients requiring large volume paracenteses more frequently than every 2 weeks (Martin 2012a, b).

The Denver Shunt is an implantable device consisting of a fenestrated peritoneal 11.5-Fr or 15.5-Fr venous catheter, and flexible pump chamber containing either one or two miter (duckbill) valves. The valves only allow flow in one direction, opening and permitting ascitic fluid to drain when the pressure of the peritoneal cavity is 3 cm H_2O higher than that of central venous pressure. The two-valve system is more commonly used as it provides better prevention of backflow and reflux, but the single-valve Denver Shunt can be useful in cases where ascitic fluid is very viscous or produced in unusually large volumes (Martin 2012b; Won et al. 2008).

Ultrasound and fluoroscopic guidance are typically used for placement of the Denver Shunt in the Interventional Radiology suite and the procedure lasts slightly over an hour (Won et al. 2008). This can be performed as an outpatient procedure, but most patients tend to be admitted for observation after the procedure to monitor for any immediate complications. Contraindications include sepsis, peritoneal cavity septation due to previous infection or surgery and dialysis for end-stage renal failure (Martin 2012a).

After setting up a sterile field, administering local anaesthetic and judicious use of sedatives to maintain moderate sedation, a 5 cm subcutaneous incision is made at the lower rib cage to create a pocket for the pump chamber. The peritoneal cavity is punctured below the costal margin above the iliac crest in the right lower abdomen, and a 0.35-inch guidewire is inserted into the dependent position of the pelvic cavity. A subcutaneous tunnel is created using a peel-away sheath inserted over a guidewire, and the peritoneal catheter is pulled through from the pump chamber. Ascitic fluid is aspirated through the peel-away sheath and the peritoneal end of the shunt is placed in the pelvis. Vascular access, commonly jugular although subclavian and saphenous venous territories have been used, is obtained under ultrasound guidance and another peel-away sheath is inserted. The venous catheter of the shunt is then pulled through and placed at the atriocaval junction. The small-calibre catheter (11.5-Fr) is preferable when using subclavian or saphenous venous access as the larger 15.5-Fr may exceed the venous lumen and result in occlusion of the native vessel. Each incision is then closed with a suture (Martin 2012a; Won et al. 2008).

After insertion, patients should be closely monitored for a minimum of 24 h post-procedure (Saif et al. 2009). The patient and/or their carer should be given an instruction manual and be taught how the shunt works, and more importantly, how to manage it. As flow through the shunt depends on position, the patient should be told to pump the shunt chamber whilst lying supine, when flow is maximum. Flow is significantly reduced when the head and shoulders are elevated to 45° and is little or absent when the patient is upright or sitting.

During the first week after insertion, however, pumping is forbidden to prevent wound contamination and complications related to sudden volume overloading, such as cardiac congestion and disseminated intravascular coagulation (DIC). After the first week, the shunt chamber should be forcibly compressed 20 times twice a day—once before rising and once before bed, to prevent debris from forming in the shunt tube, maintaining its patency. This is critical as the lack of frequency and poor technique of pumping are very common causes of shunt failure. The patient should also be given emergency contact details and followed up 2–3 weeks after shunt insertion (Martin 2012a; Won et al. 2008).

Although some studies have shown that the technical success rate is high, and that abdominal distension and respiratory difficulties are improved following shunt placement, there is still uncertainty on its insertion to manage ascites in the palliative setting. This is mainly due to its high rate of complications and the level of maintenance required, including manually pumping the shunt chamber several times a day to prevent proteinaceous debris occluding the tube (Won et al. 2008).

Complications include leakage, shunt occlusion, superior vena cava thrombosis, DIC, and deep vein thrombosis (Martin 2012b; Won et al. 2008). As such, peritoneovenous shunts are not typically first or second-line treatments and are used more as a technique to offer end-of-life symptomatic relief in patients unsuitable for other procedures (Martin 2012a).

4.4 TIPSS

Transjugular intrahepatic portosystemic shunts (TIPSS) are used to manage the sequelae of portal hypertension, predominantly secondary prevention of variceal haemorrhage and refractory ascites (Young et al. 2019; Trivedi et al. 2016). It involves intravascular insertion of a stent bridging the portal vein to the hepatic vein, providing a conduit for vascular diversion from the portal to systemic circulation, thereby reducing portal venous pressure and relieving ascites (Sankar and Moore 2017; Miraglia et al. 2017). TIPSS is also useful in managing liver cirrhosis with hepatic hydrothorax and can be used palliatively or in anticipation of a subsequent liver transplant (Martin 2012a; Young et al. 2017). Less common indications include Budd–Chiari syndrome, hepatic veno-occlusive disease, hepatorenal, and hepatopulmonary syndrome.

Patient selection should be under the direction of a hepatologist in conjunction with an interventional radiologist. Contraindications to TIPSS insertion include: primary prevention of variceal haemorrhage, severe pulmonary hypertension, congestive cardiac failure, severe tricuspid regurgitation, untreated biliary obstruction, and systemic sepsis. Relative contraindications include hepatic encephalopathy, uncorrected coagulopathy or thrombocytopaenia, and hepatic or portal venous thrombosis (Fidelman et al. 2012). Whilst a number of stratification models have been used, the currently used modified MELD score predicts mortality with those >18 having a significantly higher mortality 3 months post-TIPSS (Angermayr et al. 2003; Ferral et al. 2004).

Compared to earlier studies, stents covered with polytetrafluoroethylene (PTFE) have drastically reduced rates of shunt dysfunction and improved clinical outcome (Bureau et al. 2017). They are preferred over traditional metal stents and come in diameters of either 8 or 10 mm, with the 10 mm PTFE-covered stent (Viatorr, W. L. Gore) reported to be more effective at controlling ascites. This is thought to be because the 10 mm stent more effectively reduces the portosystemic gradient, which is the difference in pressure between the portal vein and inferior vena cava (Miraglia et al. 2017). Reported rates of ascites control post-TIPSS is approximately 74.1% (Bettinger et al. 2015) with a meta-analysis demonstrating a 7.1-fold reduction in the risk of recurrent tense ascites (D'Amico et al. 2005; Copelan et al. 2014).

Whilst a full technical description is beyond the scope of this chapter, in brief, the procedure is typically performed in the Interventional Radiology suite, and ultrasound guidance is used to puncture the right internal jugular vein (or left when the right jugular is not possible). A 5F catheter and 0.035-inch hydrophilic wire are used to catheterise the right hepatic (or middle hepatic) vein. A Colapinto needle is advanced into the portal venous branch under fluoroscopic guidance, and a syringe is used to apply negative pressure whilst the needle is withdrawn. Contrast media is injected to confirm cannulation of the portal venous branch and a 0.035-inch hydrophilic wire is used to gain access to the main portal vein. Portal venogram is performed through the catheter using a power injector, with the catheter tip in the superior mesenteric vein just before the spleno-mesenteric confluence. Right atrial, inferior vena cava pressures, and portal vein pressures are measured, and the PTFE-covered stent is deployed. Portal venogram is performed and post-TIPSS portosystemic gradient is measured again (Sankar and Moore 2017; Miraglia et al. 2017).

5 Complications

Paracentesis and catheter insertion is considered a low risk procedure that is well tolerated by patients with reported complications of bleeding, infection, leakage from the catheter site, visceral and vascular injury, tumour dissemination, and bowel perforation (Adam and Adam 2004; Stokes 2007; Fleming et al. 2009; Maleux et al. 2016).

Palliative patients typically undergo repeated paracentesis to remove recurrent ascites, and complication rates have been reported as 7.5% per patient (Rosenberg et al. 2004). A serious but rare complication includes death due to irreversible hypotensive shock, which is more common in cirrhotic liver than oncological patients. Plasma volume expanders can be given to reduce this risk as described in Sect. 4.1 (Stokes 2007).

Indwelling peritoneal catheters are commonly associated with blockage, infection, and leakage. In cases of catheter malfunction, patency of the blocked catheter can be restored using tissue plasminogen activator (e.g. alteplase) (Adam and Adam 2004; Stokes 2007). Mild cellulitis and catheter-related infections have a reported incidence of 0.9% and 5.9%, respectively, and can usually be treated with antibiotics without catheter removal (Fleming et al. 2009). In cases of bacterial peritonitis, the catheter can be removed. Catheter leakage has been reported to spontaneously resolve within 2 weeks although gross leakage into subcutaneous tissue has been reported in a morbidly obese patient (Stokes 2007; Wong et al. 2015).

Patients undergoing chemotherapy experience more minor complications like superficial infections and their catheters remain *in situ* for shorter periods. As such, it might be a consideration to insert indwelling peritoneal catheters only after chemotherapy is completed or closely monitor these patients if they are inserted (Tapping et al. 2012).

Peritoneovenous shunts have an overall complication rate of up to 31%, which includes ascites leakage, shunt infection, venous thrombosis, and DIC (Won et al. 2008). The risk of post-shunt coagulopathy can be reduced by discarding most of the ascitic fluid before the shunt is inserted, which also reduces the risk of other complications such as post-procedure variceal bleeding and delayed wound healing (Won et al. 2008; LeVeen et al. 1987). To avoid venous catheter thrombosis, low-dose warfarin can be administered (Bratby et al. 2007).

Other catheter-related complications in peritoneovenous shunt insertion, such as kinking and occlusion, occur in one third of patients and may require revision or removal (Won et al. 2008). Strict adherence to manufacturer instructions such as post-procedural maintenance (i.e. pumping of the pump chamber daily) can help to reduce obstruction and maintain long-term patency of the shunt (Martin 2012a; Won et al. 2008).

TIPSS may result in a number of high impact adverse complications including gastrointestinal bleeding, spontaneous bacterial peritonitis, and hepatorenal syndrome, which have an incidence of 8%, 2%, and 4.6% respectively (Salerno et al. 2007). Hepatic encephalopathy following TIPSS is a potentially serious complication secondary to the shunt, impairing the liver's ability to filter toxins. With a reported rate of 41–44% post-procedure, those with advanced cirrhosis and a history of recurrent confusion episodes are more susceptible (Sankar and Moore 2017; Miraglia et al. 2017).

Episodes of hepatic encephalopathy can occur within weeks post-TIPSS and is characterised by confusion, disorientation, obtundation, abnormal sleep patterns, and overall alterations in quality of life. Management includes general and nutritional support, identification, prevention, and treatment of precipitating events (e.g. dehydration, constipation, sedative use, sepsis). Non-absorbable disaccharides (e.g. lactulose) and non-absorbable antibiotics (e.g. rifaximin) are given initially, with the ultimate treatment being liver transplant (Madoff et al. 2004; Pereira et al. 2015). In the event of refractory hepatic encephalopathy or progressive hepatic dysfunction, endovascular shunt reduction may be considered.

6 Follow-Up

All patients should be monitored for any immediate complications before discharge. Depending on which technique has been used to drain the ascitic fluid, after care will differ.

Patients who have the PleurX catheter inserted should have their initial drainage of ascites in hospital under supervision and be taught how to manage ascitic drainage using the vacuum bottles. Drainage is limited to 500 mL per 12 h to avoid hypovolaemia and hypokalaemia. Early and frequent drainage is recommended over waiting until the ascites accumulates such that the abdomen becomes distended and uncomfortable. Regular checks with a community nurse are beneficial to ensure correct practice and contact details given to the patient in case of any problems (Tapping et al. 2012).

At the 2–3 week follow-up, the peritoneal shunt is evaluated to ensure patency. Difficulty compressing the shunt chamber may indicate an obstruction in the venous limb or coagulated blood in the shunt chamber, whilst slow refill of the shunt chamber after compression suggests obstruction in the peritoneal limb. If the shunt needs to be accessed for diagnostic or therapeutic purposes, a non-coring needle (e.g. Huber or 18-gauge Chiba) can be used to inject contrast under fluoroscopic imaging to identify any blockage. If the blockage is unresolvable by flushing or re-priming the system, a guidewire can be inserted to dislodge the debris. Any evidence of consumptive coagulopathy, DIC, or fluid overload are also sought (Martin 2012a).

Following a TIPSS procedure, a Doppler ultrasound is performed prior to discharge to check for the presence of a large volume of ascitic fluid and provide baseline parameters of portal and intrastent flow velocity. Follow-up intervals are tailored to each individual patient but a reasonable schedule includes a Doppler ultrasound check at 1 month, 3 months, and 6 monthly thereafter to allow early identification of TIPSS dysfunction (Young et al. 2019; Miraglia et al. 2017).

7 Comparison of Techniques

Repeated large volume paracenteses have been reported to have a similar complication rate (per patient) of 7.5% to that of patients who have a PleurX indwelling catheter inserted. Thus, inserting an indwelling catheter can be beneficial for such patients, as it prevents them from requiring frequent hospital visits for repeated ascitic drainage (Rosenberg et al. 2004).

TIPSS is often considered in patients with refractory ascites due to liver cirrhosis, with a favourable recurrence rate of 42% compared to 89% following paracentesis. This is offset by the inherent risks of TIPSS compared to simple paracentesis, costs and risk of hepatic encephalopathy, although the cumulative probability of developing the first episode of hepatic encephalopathy is similar for both (Salerno et al. 2007).

A prospective randomised trial of 32 patients comparing the efficacy of TIPSS to peritoneovenous shunts in the treatment of medically intractable ascites concluded that insertion of a peritoneovenous shunt was better at controlling ascites at 1 month compared to TIPSS insertion (73% vs 46%). However, the long-term efficacy at 3 months favoured TIPSS insertion, with 85% of patients having their ascites controlled, compared to 40% in those who had a peritoneovenous shunt. Shunt patency was also higher in the TIPSS cohort (31.1 months) compared to the peritoneovenous shunt cohort (13.1 months) (Rosemurgy et al. 2004).

In addition to technical success, other factors such as cost and local resources should be considered, as these can vary depending on country and setting. For example, NICE estimates that the PleurX system saves the NHS £1051 per patient compared to repeated inpatient paracentesis, whilst an American study has estimated paracentesis to be costlier only when performed more than 9 times if repeated every 10 days, removing 5 L each time (White and Carolan-Rees 2012; Bohn and Ray Jr 2015).

8 Conclusion

Ascites is common in both non-malignant and malignant conditions and tends to cause pain, discomfort and impaired mobility in palliative patients. Drainage of ascitic fluid using interventional procedures such as repeated large volume paracentesis, indwelling peritoneal catheters, peritoneovenous shunts, and TIPSS can dramatically relieve these symptoms and improve quality of life.

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Abscesses

S. Z. Tang and Raymond J. H. Chung

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S. Z. Tang (✉) · R. J. H. Chung
Department of Diagnostic Imaging,
National University Hospital, Singapore, Singapore

Department of Diagnostic Radiology,
Khoo Teck Puat Hospital, Singapore, Singapore
e-mail: Si_Zhao_TANG@nuhs.edu.sg;
chung.raymond.jh@ktph.com.sg

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P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_28

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Abstract

Image-guided drainage of the abscesses confined within thorax, abdomen, and pelvis is increasingly being utilised and incorporated in the management strategies for patient who developed infective complications. The minimal invasive nature of these techniques has obviated much of the need for open surgical drainage which generally has higher morbidity risk. This chapter will outline the methodological approach for image-guided drainage procedures, with various adjunctive techniques to increase the success rate of procedure. Rationale and method for special drainage route utilising the interorgan spaces and organ transversal routes will be described as well.

Abbreviations

aPTT	Activated partial thromboplastin time
ASA	American Society of Anesthesiologists
CT	Computed tomography
Fr	French
G	Gauge
INR	International normalised ratio
IR	Interventional radiology
LMWH	Low-molecular-weight heparin
MPR	Multi-planar reconstruction
MRI	Magnetic resonance imaging
NOACs	Novel anticoagulants
SIR	Society of Interventional Radiology
tPA	Tissue plasminogen activator
US	Ultrasonography

1 Introduction

Abscess is a confined collection of pus in a tissue, an organ, or a confined space. An abscess can be characterised by three components: a central core consisting of necrotic tissue, leukocytes and oedematous fluid, a peripheral halo of viable neutrophils, and all enclosed in a 'capsule' with vascular dilatations and proliferation of fibroblasts (Kumar et al. 2018).

Image guided, minimally invasive drainage techniques, with their associated lower morbidity and mortality compared to the traditional open surgical drainage, are widely accepted as the first-line treatment of abscesses in the thorax, abdomen, and pelvis. As with other image-guided interventional procedures, these should be planned and conducted in a sequential fashion beginning with pre-procedure planning, including clinical evaluation of the patient and anatomical mapping, and ends with the post-procedure management to pre-empt possible complications (Carberry et al. 2016).

In this chapter, a staged approach to both routine and complex abscesses drainages will be described to facilitate the understanding of these concepts. The choice of drainage devices, recommendation on appropriate imaging modality guidance, adjunctive techniques to facilitate accessing an abscess in arduous locations and/or reduce peri-procedural risk, and selected post-procedural issues will be covered.

2 Preprocedural Planning, Preparation, and Contraindications

2.1 Planning

Appropriate patient selection is pivotal to both technical and clinical successful outcome. Firstly, one must consider whether the drainage of the abscess will affect the clinical course of the patient. If this is affirmative, will the benefits of the drainage procedure outweigh the potential associated risks? For example, if the abscess is too small or yet to have a walled-off pus collection on imaging, then the risks may outweigh the

benefits and alternatives, such as continued medical therapy with follow-up imaging to guide delayed drainage, may be more appropriate. Additional indications for drainage of suspected infected collections includes the need for fluid characterisation and also as a bridge to definitive management when the patient's clinical condition improves.

2.2 Preprocedural Preparation

As with any other invasive procedures, appropriate explanation regarding the rationale of the procedure, its associated risks versus benefits, and alternative choices should be provided to the patient. Most abscess drainage procedures are performed with local anaesthesia and supplementary conscious sedation as required. General anaesthesia is more often considered in the setting of young children, patients who are uncooperative or with other significant comorbidities (Mohan and Swerky 2018). To reduce the risk of aspiration of gastric contents, especially in the setting of pharmacological sedation, ASA guidelines recommend fasting of 6 and 2 h for a light meal and clear fluids, respectively (Practice guidelines for preoperative fasting 2017). Intravenous access should be available prior to procedure.

2.3 Contraindications

Contraindications to image-guided minimally invasive drainage of an abscess include lack of a safe pathway from significant viscera or vasculature, for example, transgression of interposed bowel may result in bacterial translocation and infected fistula formation, uncorrectable coagulopathies, severely limited cardiopulmonary function and lack of patient cooperation (Wallace et al. 2010).

Relative contraindications include sterile fluid collections which do not have the imaging features of an abscess and have the potential to become secondarily infected following catheter drainage, or tumour abscess which may lead to needle track tumour seeding (Mohan and Swerky 2018).

3 Laboratory Evaluation of Coagulation Status, Anticoagulation Management and Antibiotic Consideration

3.1 Evaluation of Coagulation Status

Percutaneous drainage procedures for intra-abdominal, chest wall, or retroperitoneal abscesses according to the SIR are classified as procedures with moderate risk of bleeding. Recommendations for preprocedural evaluation of coagulation status include serum INR (target value <1.5) and platelet count (transfusion is recommended for platelet count <50,000 μL). aPTT is recommended for patient on intravenous unfractionated heparin; however, the consensus for correction is not firmly established (Patel et al. 2012). Those with chronic kidney disease/end-stage renal failure may have an increased risk for bleeding that is not routinely reflected by the usual preprocedural lab values, due to the effect of the underlying conditions on platelet function and the coagulation cascade (Hedges et al. 2007).

3.2 Management of Anticoagulation

Commonly encountered anticoagulative medications include aspirin, clopidogrel, and heparin. Consensus guidelines do not recommend a need to withhold aspirin whilst clopidogrel should be discontinued for at least 5 days prior to the procedure. For patients on therapeutic dose of LMWH, one dose should be withheld 12 h prior to the procedure (Patel et al. 2012).

NOACs are rising in popularity for clinical use and include dabigatran (inhibits factor II, i.e. thrombin), rivaroxaban and apixaban (both inhibits factor Xa, rate-limiting factor in thrombin production and amplification). Recommendations are for dabigatran to be withheld 24 h, whilst rivaroxaban and apixaban are omitted 12–24 h prior to procedure. In those with renal impairment, it is recommended to extend the period of

omission by 12 h due to reduced renal excretion (Crockett et al. 2012).

3.3 Consideration of Antibiotic Therapy

Antibiotic prophylaxis is usually recommended for IR procedures that are considered as clean-contaminated (e.g. embolisation with intent to create infarction or nephrostomy tube placement in a patient with sterile urine), contaminated (entry into an inflamed or colonised GI or GU tract without frank pus), or dirty (abscess drainage) as per National Academy of Sciences/National Research Council surgical wound classification (Berard and Gandon 1964).

Antibiotic prophylaxis in IR serves a slightly different purpose compared to prophylaxis of the open surgical wound, in that it is to reduce the risk of infection resulting from the communication created by a needle or catheter between the infected site and the bloodstream (Zarrinpar and Kerlan 2005).

Most patients referred to IR for percutaneous abscess drainage have typically already been commenced on antibiotic therapy. However, if a patient is planned for percutaneous abscess drainage without concurrent antibiotic treatment, initiation of antibiotic therapy is recommended due to risk of cavity rupture and content spillage during wire or needle manipulation (Lorber and Swenson 1975).

The updated SIR Standards of Practice 2018 guidelines (Chehab et al. 2018) suggest single-agent empirical regimens for intra-abdominal abscesses, such as meropenem, imipenem/cilastatin, doripenem, and piperacillin/tazobactam as these are frequently polymicrobial in origin. For pleural abscesses, antibiotic regimens (e.g. piperacillin/tazobactam or amoxicillin/clavulanic acid) to cover for Streptococcus, Staphylococcus, Enterococcus, and Pseudomonas species are suggested. Initiation of antibiotic agents is now considered as empirical treatment instead of prophylaxis solely and should be continued after drainage procedure (Chehab et al. 2018). The use of antibiotic prior to drainage usually does not interfere with the culture and sensitivity of drainage fluid (Mohan and Swerky 2018).

4 Selection of Imaging Guidance Modality

4.1 Ultrasonography (US)

US has superior soft tissue contrast as compared to unenhanced CT. It allows for real-time visualisation of the abscess collection, surrounding anatomical structures, needle and catheter placement which can expedite procedures without compromising safety. This is particularly valuable for collections that are in close proximity to the lungs, bowel loops, or vascular structures. The portability, absence of ionising radiation, and lower capital cost of US equipment compared to CT are additional advantages.

In contradistinction to CT guidance where the operator is restricted to an axial or near-axial approach, the US transducer can be angled in any plane, allowing a more flexible approach.

The limitations of US visualisation include patient body habitus, probe-handling experience of operator, need of an appropriate acoustic window for target visualisation, inability to penetrate bone and structures that contains air (e.g. bowel, lung, or gas within the abscess).

4.1.1 Techniques

US-guided drainage is commonly performed under the free-hand method, in which a single operator operates both the US transducer probe and access needle/drainage devices. A two-person technique, in which the sonographer will manipulate the transducer whilst the needle is being advanced by the radiologist has also been described.

The US transducer with the highest frequency at the required sonographic depth will provide the optimal spatial resolution and ideally allow needle visualisation throughout its entire trajectory. Optimisation of machine settings including overall gain, TGC (time gain compensation) curves and focal zones are tailored to the depth of the abscess. Harmonic imaging can aid in

reducing the detrimental artefacts and improving the image contrast of abscess to increase conspicuity.

Techniques to improve visualisation on US-guided drainage include bouncing the needle with B-mode or colour Doppler imaging to identify the needle tip, and gently scoring the needle tip with a rough Kelly clamp (Carberry et al. 2016).

4.2 Computed Tomography (CT)

CT provides good spatial resolution and significantly larger field of view in comparison to US. It provides a more precise visualisation of abscess location in relation to adjacent visceral structures and reduces the likelihood of mistaking fluid-filled bowel loops for fluid collections. In addition, bones and air-containing structures (e.g. bowels and lungs) do not interfere with abscess visualisation.

The imperfection of CT includes ionising radiation exposure, absence of real-time guidance, and reduced sensitivity in identifying loculations within the abscess compared to US. CT-guided drainage is often limited to the axial plane which can be challenging for abscesses in which the point of access and abscess location do not reside at the same level of the craniocaudal axis.

4.2.1 Techniques

Techniques to improve accuracy and safety of CT-guided drainage include:

1. Bowel opacification: using oral or rectal contrast (such as Gastrograffin) to better discern the abscess from adjacent bowel loops (Mohan and Swerky 2018).
2. Utilising a large-bore CT scanner to allow extra gantry space for placement and manipulation of the drainage devices, or if the patient has a large body habitus (Carberry et al. 2016).
3. Gantry angulation up to 30° from vertical to optimise the needle path and circumvent structures such as lung bases (Carberry et al. 2016).
4. Optimising patient position to ensure patient stability, comfort, and ease of percutaneous access.
5. 'Dead reckoning' technique in which only the needle tip is visualised and advanced judiciously, with the rest of the needle angled out of the gantry.

Last but not least, combining both US and CT guidance can significantly hasten the procedure whilst maintaining safety, as this has the combined advantages of both modalities and compensates for their individual limitations.

5 Procedure Preparation and Aspiration

The appropriate image guidance technique, drainage route, and patient positioning is predominantly based upon the prior imaging studies with additional reference to patient-specific factors that may make certain positions more problematic, e.g. lying prone in a patient with recent laparotomy wounds.

Safe route for skin puncture, needle angle, drainage pathway, and percutaneous distance to collection are identified and measured.

The shortest possible drainage pathway without transgressing vital structures is planned. Extraperitoneal approach is preferable to avoid peritoneal contamination. The colon and pancreas are generally avoided due to the risk of superinfection and pancreatitis, respectively. Transgression of liver, kidney, stomach, and small bowels have been described for needle aspiration solely. However, these organs should also be avoided in catheter drainage to reduce the risk of fistula formation.

For pelvic abscesses, the anterior approach is usually less favoured due to anatomical complexity hence transgluteal, transvaginal, or transrectal routes may be considered. The details of these approaches will be elaborated in the sections below.

Needle aspiration of the fluid collection is often used to decide whether the collection is infected or sterile prior to catheter placement.

Only a few millilitres of collection should be aspirated to prevent collapse of the fluid cavity. The colour, smell, viscosity, and turbidity of aspirate will provide additional information in the determination of the presence of an abscess. Catheter placement is generally indicated for purulent collection; however, needle aspiration until dry is another viable alternative in certain clinical situations in which recurrence of the collection is unlikely. The acquired fluid samples are usually sent for Gram stain, culture, and sensitivity as clinically indicated, or subject to further laboratory tests as requested by clinician teams.

A supplementary technique akin to surgical lavage may be employed, which involves irrigation of the abscess cavity with aliquots of 0.9% saline to encourage the drainage of abscess with thick debris (Gervais et al. 2004a). The volume used for irrigation is recommended to be smaller than the drained abscess to avoid an increase in intracavitary pressure which may predispose to bacteraemia and a septic shower.

6 Catheter Placement

Catheter placement is usually preferred over needle aspiration for definitive treatment. The drainage catheter is secured in position for several days, especially if the aspiration material appears infected, has pus-like appearance or if the patient is septic (Ryan et al. 1998).

Contraindications for percutaneous aspiration only without catheter placement include abscess with communication to bowel, biliary, or urinary tracts. Percutaneous aspiration solely for these collections is generally futile as there is often re-accumulation (Maher et al. 2004).

6.1 Catheter Insertion and Placement Techniques

The two main methods for catheter placement into an abscess are the trocar and Seldinger techniques.

6.1.1 Trocar Technique

This involves a catheter mounted on a sharp trocar and inserted directly into the abscess without the use of a guidewire. The trocar components are as shown in Fig. 1. A small gauge guiding needle may be positioned along the desired access path to the abscess to act as a secondary guide of optimal trajectory.

This technique allows rapid catheter deployment, which is useful if the temporal window for sedation is limited. However, this technique is less amenable to repositioning of the drain after deployment.

In uncomplicated abscesses with suitable size in easily accessible location, catheter placement via trocar technique under US guidance offers the simplest and quickest way to achieve

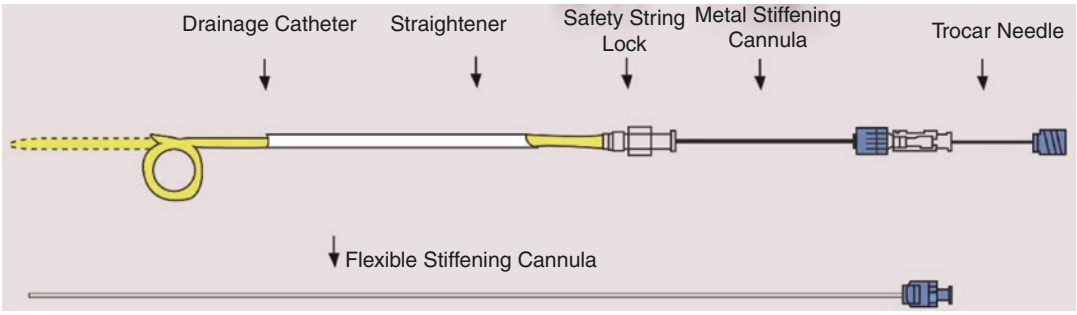

Fig. 1 Components of a trocar drainage catheter which includes trocar needle stylet, metal stiffening cannula, pigtail catheter, catheter tip before and after trocar retrieval. Image adapted from Drainage & Nephrostomy Catheter Sets: One Step Pigtail with Safety String Loc, Biometrix Ltd (Biometrix Ltd n.d.)

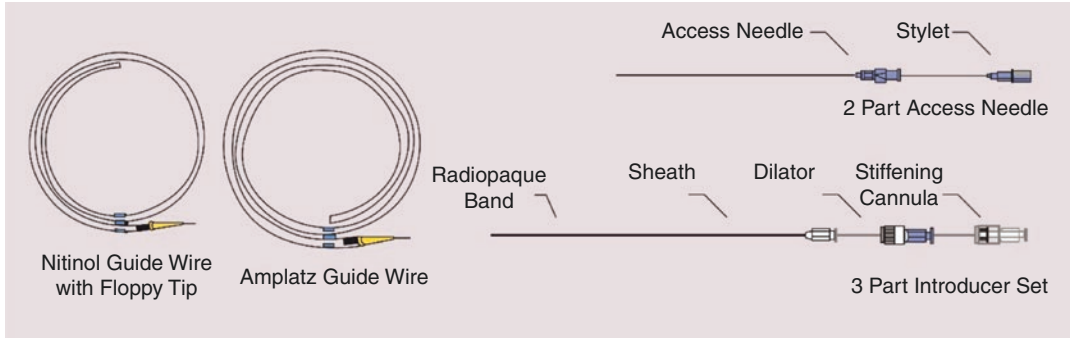

Fig. 2 Components of Seldinger drainage catheter set which includes access needle with stylet, guidewire with floppy/stiff tip, introducer set with dilator. Image adapted from Drainage Catheter Insertion Set with Amplatz Guidewire, Biometrix Ltd. (Biometrix Ltd n.d.)

percutaneous abscess drainage. Fluoroscopy imaging augmentation can be utilised if only a limited portion of the abscess is depicted on US, or a more precise positioning is required due to proximity of adjacent vital structures such as major blood vessels.

6.1.2 Seldinger Technique

The Seldinger technique is thought to have a better safety profile and hence is more commonly utilised in drainage catheter placement (Mohan and Swerky 2018). The catheter components are as shown in Fig. 2.

This involves introduction of a hollow needle into the abscess cavity, followed by guidewire insertion through the needle (to serve as a guidance for catheter drainage pathway). The needle is removed, and the percutaneous track serially dilated via Teflon dilators over the guidewire. The drainage catheter is then railed over the guidewire into the abscess cavity.

Another advantage of this technique is the ability to manipulate the wire into an optimum location for catheter deployment. This is especially for abscesses in restricted locations, such as in the subphrenic region. Disadvantages include the multiple steps required for dilatation to create a suitable percutaneous drainage pathway with potential buckling or kinking of the wire, and the reduced operating space in small abscess collections due to leakage during needle removal and dilatations.

US with adjunct fluoroscopy imaging is useful for monitoring wire manipulations during catheters placement via Seldinger technique. If the abscess contains air, obscured by overlying bowel gas or is in deep locations such as pelvis, in which US will only yield limited information, CT guidance should be considered. CT guidance can be performed either with standard incremental acquisition of a few contiguous axial images in the anatomical region of interest or with CT fluoroscopy.

6.2 Selection of Needle Systems and Catheters

Commonly employed initial needle access systems in the Seldinger technique include 18-G angiographic needles and 19-G needles sheathed in 5-Fr catheters which will accommodate the 0.035 inch guidewire used for subsequent catheter deployment.

For those with a narrower window of access, a “skinny” (21- or 22-G) needle may be considered that accommodates an 0.018-inch guidewire. Upon successful entry into the collection, this can be upsized to a larger calibre wire or left in situ as an insurance wire.

Larger calibre catheters (12- to 14-Fr) are advocated in larger abscesses or those containing substance of higher viscosity.

Spread-out or longitudinal abscesses may be more suitably drained by coilable catheter with extended multiple side-holes.

7 Catheter Fixation and Management

There are two means of catheter retention: an internal retention mechanism and an external fixation device.

Locking pigtail catheters are an example of an internal retention design in which a string courses through the catheter and draws the distal catheter tip into a loop, "pigtail" configuration, preventing inadvertent removal. The string is designed to snap under excessive tension, thus reducing the risk of catheter rupture inside the patient.

Drainage catheters may then be taped or sewn to a device that adheres to the skin which obviates the need of suturing the catheter directly to the patient's skin. This method reduces the skin irritation caused by sutures and possibly infection rates as well (Yamamoto et al. 2002).

The catheter should ideally be flushed twice or thrice daily with small amount of normal saline solution. This is to encourage drainage by clearing any adherent plugs or encrustations within the drainage tube.

Regular assessment of the catheter should be performed to ensure that the catheter tip remains in an optimal position within the abscess, ensure drainage tube patency and promote regular review of the drainage fluid appearance, access site, and dressing.

A fistula should be suspected if there is change in the effluent characteristics, and further imaging may be warranted. Fistulogram or abscessogram can be performed via the catheter if there is clinical suspicion of a fistula with no concurrent sepsis. This examination should be deferred in the presence of sepsis to avoid further increase in intracavitary pressure, which may further exacerbate bacteraemia and sepsis.

8 Special Approaches for Difficult Abscess Locations

Abscesses are sometimes located in difficult locations with multiple intervening vital structures limiting the traditional percutaneous access pathway.

8.1 Deep Pelvis

There are numerous intervening structures in the pelvis which preclude anterior or lateral approaches due to inadequate margin of safety. The main intervening structures include surrounding pelvic bones, urinary bladder (anterior aspect), bowel (anterolateral aspect), and large iliac vessels and nerves (in both lateral aspects). Several approaches have been devised to circumvent these obstacles. These include transgluteal (CT-guided), presacral space (CT-guided), transvaginal and transrectal (US-guided) approaches.

8.1.1 US-Guided Transvaginal and Transrectal Approaches

US-guided transvaginal and transrectal drainages offer safe access to deep-seated abscesses within the vaginal or rectal vicinity, which are usually inaccessible via a percutaneous route (Varghese et al. 2001). These are usually performed with an intracavitary US probe placed within the vagina or rectum. High-frequency intracavitary US probes can depict the abscess and its internal architecture, with higher resolution than CT. The needle and drainage catheter can be mounted on the intracavitary probe to achieve satisfactory real-time US guidance.

Possible limitations of this route of access include obscuration of the target abscess by adjacent bowel loops or gas within the abscess cavity (Saokar et al. 2008; Taşar et al. 2004) and the potential risk of rectal wall or vaginal vault perforation, the latter with subsequent retrograde infection of the reproductive tract (Maher et al. 2004; Harisinghani et al. 2002).

Transvaginal US-guided drainage of pelvic abscesses is useful for deep-seated abscesses located close to the vagina and is usually performed with the patient in lithotomy position. The major structures adjacent to this route especially the urinary bladder should be identified and avoided to prevent vesicovaginal fistula formation. Excessive transducer pressure is best avoided to limit urinary bladder compression and obscuration, which would increase the risk of inadvertent urinary bladder transgression. This is likewise for other intervening structures such as bowel. Abscesses within the presacral, ischiorectal spaces and higher within the pelvis are less favourably drained from this location due to intervening anatomical structures (Varghese et al. 2001). For the transvaginal approach, the trocar method is favoured over the Seldinger technique due to reduced procedural time and, as the guidewire position is more difficult to monitor on US, the risk of guidewire kinking and access loss is higher. After optimal placement is achieved, the drainage catheters are usually sutured to the medial aspect of the thigh (Maher et al. 2004).

Transrectal US-guided abscess drainage is usually used in male patients for abscesses anterior (e.g. prostate abscesses) and posterior to the rectum, i.e. presacral space or ischiorectal fossae. For transrectal approach, the patient ideally should be placed in the left lateral decubitus position. The trocar technique is preferred over the Seldinger technique for transrectal approach, with similar rationale as the transvaginal approach as stated above. Combined fluoroscopic guidance after initial US-guided access is helpful in monitoring guidewire position and catheter deployment.

8.1.2 CT-Guided Transgluteal Approach

CT-guided transgluteal approach through the greater sciatic foramen was first described by Butch et al. in 1986 (Butch et al. 1986), performed with patient in prone or decubitus position. An access site close to the sacrum at the level of the sacrospinous ligament is preferred to avoid the more laterally sited sciatic nerves and associated vessels (Ryan et al. 1998; Harisinghani et al. 2002). The sacral plexus, superior and inferior gluteal vessels branches lie adjacent to the piriformis muscle and a transpiriformis approach is associated with increased risk of catheter-related intraprocedural and post-procedural pain (Harisinghani et al. 2002; Soyer et al. 2005). Consequently, an infrapiriformis muscle approach is also advocated whenever possible.

Craniocaudal angulation of the CT gantry can facilitate transgluteal abscess targeting whilst maintaining direct visualisation of the needle/catheter in situations where the skin access site is at a different level to the abscess location on the traditional axial anatomical slices. This may either be due to pelvic bone preventing direct access or neighbouring visceral structures that need to be avoided (Gervais et al. 2004a).

This approach is also favoured over transrectal access for drainage of indeterminate fluid collections, as it allows sample acquisition under aseptic technique (Gervais et al. 2004a).

Despite the proximity of the sciatic nerve and vessels for transgluteal approach, the risk of injury to the neurovascular bundle is considered rare although patient ambulation may be limited post procedure (Maher et al. 2004; Harisinghani et al. 2002; Robert et al. 2016).

8.2 Upper Abdomen

8.2.1 Subphrenic Regions (Subcostal and Intercostal Approaches)

In addition to the usual anatomical barriers to safe percutaneous abscess, interventions in the subdiaphragmatic upper abdomen are at risk of pleural transgression and associated complications. As the anterior pleural reflection ends cephalad to the posterior reflection, opting for the lowest and most anterior access route feasible minimises this risk. In this vein, a subcostal anterior approach is preferred over an intercostal approach.

An oblique trajectory from access site to destination is therefore usually necessary. With current CT post-processing technology, an oblique approach can be planned using MPR techniques for multislice CT (Kim et al. 2008; Xiang et al. 2017).

An inferior subcostal skin access site is punctured under US- or CT guidance, followed by cephalad angulation of the needle, then advancement of the catheter into the subphrenic collection via Seldinger technique under CT/fluoroscopic guidance, with angulation of gantry if required.

Despite the techniques described above, pleural transgression still occasionally occurs. In this event, the patient should be monitored closely for pneumothorax or pleural effusion on post-procedure CT and serial radiographs of the chest. Chest tube placement is usually indicated for pleural effusion due to potential complication of an empyema. Pneumothorax should be treated with a chest tube only if symptomatic or if there is increase in size or persistent significant pneumothorax despite 2–3 days of observation.

8.3 Epigastrium, Pancreatic and Peripancreatic Abscesses

These abscesses are usually drained under CT guidance with Seldinger technique because of its depth and proximity to vital structures. The major consideration for abscess drainages in these regions is to avoid transgression of bowels, major mesenteric, peripancreatic, or retroperitoneal vessels (Lee et al. 1998). The anterior approach for posterior epigastric region is often complicated by the overlying stomach, whilst the lateral approach may be obscured by the spleen, and the posterior approach requires negotiation past the bones and kidneys. Whilst some organs may be amenable to trans-visceral access, the spleen and pancreas are generally avoided due to the risk of haemorrhage and pancreatitis, respectively. Some of the commonly employed access routes (gastrosplenic, left anterior pararenal space, paravertebral, right anterior pararenal space) are depicted in Figs. 3 and 4.

8.3.1 Gastrocolic Approach

This gastrocolic route, between the stomach and transverse colon, is useful for abscess drainage within or adjacent to the pancreatic head. During pathological collection, formation in this region, the gastrocolic ligaments may be stretched and displaced providing a viable access route.

8.3.2 Left Anterior Pararenal Space Approach

This approach is commonly used to drain pancreatic tail region abscesses. Collections in this pancreatic tail region extend into the left pararenal space and displace the colon anteriorly.

8.3.3 Gastrosplenic Approach

This approach navigates through the gastrosplenic ligament to access abscesses in the pancreatic body and tail.

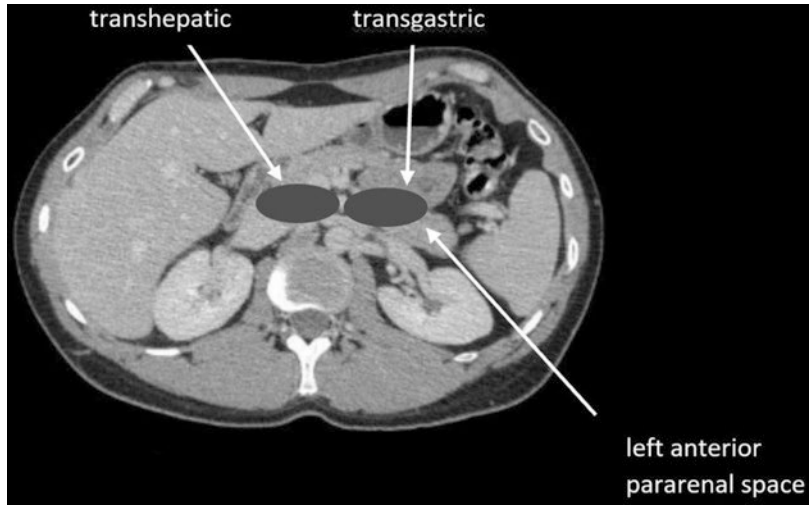

Fig. 3 Depiction of transhepatic, transgastric, and left anterior pararenal space approaches

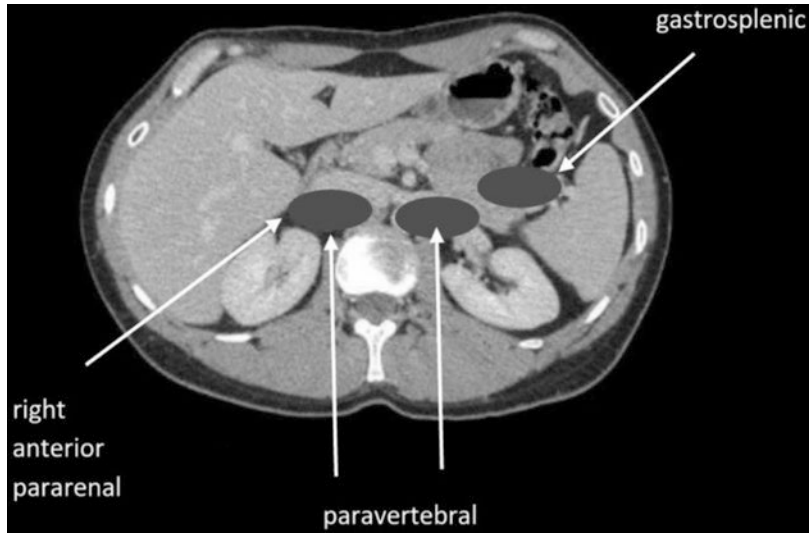

Fig. 4 Depiction of gastrosplenic, paravertebral, and right anterior pararenal space approaches

8.3.4 Transhepatic Approach

Occasionally, even with the use of CT and alternative routes, a collection cannot be accessed without traversing an intervening organ. In the appropriate clinical conditions and following patient-specific risk assessment, the intervening organ may be purposefully traversed with a catheter for drainage of the deeper collection. For example, if access via the gastrocolic ligament is not possible, a transhepatic approach is often used to drain an abscess in the pancreatic head region. The liver is one of the organs that is considered safe to be traversed for treatment of epigastric abscess. The safety and efficacy of this approach was first described in 1985 by Mueller et al. (1985) and several subsequent studies (Yamakado et al. 2010; Ciftci et al. 2012; Zhao et al. 2018).

For transhepatic approach, the coagulation parameters should be normal before procedure commencement. It is essential for the planned catheter course through the liver parenchyma to be as short as possible, avoid central transgression of liver (especially porta hepatis) and diverted away from major blood vessels, dilated biliary ducts, and other uninvolved viscera such as the gallbladder. Hepatic segment III and VI are recommended as the optimal transhepatic access route owing to the absence of major hepatic vasculatures and biliary branches (Zhao et al. 2018). The catheter side-holes should be placed within the abscess cavity to avoid cross-contamination of the adjacent liver or biliary tract.

8.4 Visceral Abscesses (Include Hepatic, Splenic, and Renal Abscesses)

For liver abscesses, the indication for drainages is usually due to size factor, or if refractory to antibiotic therapy (Theodore 2008). Sometimes, this is performed to avoid rupture and leakage of the abscess contents into the thorax or peritoneum if it is of significant size or located close to the hepatic surface (e.g. in the subdiaphragmatic region) (vanSonnenberg et al. 1985).

Splenic abscesses are considered very rare and are usually associated with immunosuppression, caused by infected haematoma (usually trauma-related) (Ferraioli et al. 2009). Drainage is usually amenable in large splenic abscesses. Several studies have reported successful drainage of splenic abscesses (Lucey et al. 2002; Thanos et al. 2002; Sammon et al. 2012), and there is a progressive trend towards conservative management of infected splenic haematoma by drainage (Singh et al. 2012).

Renal abscesses are usually complications from pyelonephritis or nephrolithiasis, or due to

haematogenous seeding (Lim and Ng 2011). As with hepatic and splenic abscesses, the indication for drainage is usually due to size factor or if refractory to antibiotic therapy alone.

9 Post-procedure Management

Flushing of the catheter is recommended every 6–8 h to maintain tube patency; frequency should be increased for viscous collections. Approximately 5 mL 0.9% normal saline is directed towards the collection whilst an equal amount is flushed towards the drainage bag. Viscous abscesses are better treated with active negative pressure drainage, whilst passive drainage is usually adequate for serous pleural effusions and ascites.

No further imaging is required if the clinical course improves and catheter output correlates with estimated abscess volume, declining to less than 10–20 mL daily. If the patient again presents with clinical suspicion of sepsis (persistent fever, pain, or leucocytosis) despite prior drainage, further imaging may be warranted. Persistent high output of drainage (>50 mL) after 4 days of catheter placement should raise suspicion for fistula formation, and further imaging evaluation such as abscessogram or fistulogram is usually indicated.

CT is the preferred modality to monitor the adequacy of drainage and development of new abscesses. Catheter removal is appropriate following resolution of the abscess with no further drainage output. In the event of persistent liquefied abscess despite optimal placement of a patent catheter, exchange to a larger calibre catheter may be considered.

9.1 Adjunctive Thrombolytic Therapy

Less commonly used in general clinical practice, adjuvant thrombolytic therapy has been employed to break down fibrin and facilitate drainage when there is persistent low output due to abscess content with high viscosity. 4–6 mg of tPA diluted in 50 mL of normal saline can be used twice daily for 3 days, with catheter clamped for 30 min after tPA instillation, followed by passive gravity drainage (Beland et al. 2008). The administered volume should never exceed the volume of collection to avoid increase in intracavitary pressure and further exacerbate bacteraemia and a septic shower.

10 Complications

Major complications as defined by SIR Standards of Practice Committee 2010 (Wallace et al. 2010) include significant haemorrhage, perforated hollow viscera due to transgression, pleural complications (e.g. pneumothorax, haemothorax), septicaemia, and peritonitis (Valji 2006).

Significant haemorrhage usually occurs secondary to inadvertent vascular structure injury and often necessitates prompt angiographic intervention.

For inadvertent hollow viscera perforation, the morbidity rate depends on the puncture site (trans-enteric or trans-colonic), clinical status of the patient and whether catheter deployment has been made. Inadvertent catheter placement through the small bowel is reported to be less morbid as compared to large bowel. For inadvertent trans-enteric drainage, conservative management can be considered in the form of bowel rest, broad-spectrum antibiotic coverage and supportive treatment, provided there is no suspicion for peritonitis/bowel obstruction. Inadvertent transcolonic drainage has high risk for life-threatening peritonitis and sepsis, hence warrants immediate surgical consultation. Early surgical consultation should also be made if patient develops signs of peritonitis or bowel obstruction following transenteric drainage. Withdrawal of the drainage catheter without primary surgical repair is possible, and usually deferred until development of a mature enterocutaneous tract. This can be affirmed by contrast injection through the drainage tube (“over-the-wire tractogram”) under fluoroscopic imaging. Depending on operator preference, gradual withdrawal of the catheter

over days to weeks can be adopted to allow time for the enterocutaneous tract to close (Lorenz and Thomas 2006).

Septic shock is reported in 1–2% of patients during drainage procedures (Wallace et al. 2010). Initial management is predominantly supportive including airway control, fluid resuscitation, and aggressive antibiotic therapy (Rhodes et al. 2017; Howell and Davis 2017).

Minor complications include pain at the access site, self-limiting bleeding, localised infection at catheter site, and peri-catheter leak. Complications related to the drainage catheter include kinking, occlusion or migration of the catheter, which can be minimised with accurate procedure techniques and meticulous catheter monitoring.

11 Conclusion

Image-guided percutaneous drainage is a safe and effective treatment for patients with mediastinal, intra-abdominal, or pelvic abscesses/collections, as evidenced by reported success rate of more than 90% (Wallace et al. 2010; Gervais et al. 2004b). This is predicated upon appropriate patient selection, technique of insertion and post-procedural care.

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Part VIII

Miscellaneous

Treatment of Fistulas

Kristen Alexa Lee, Nanda Venkatanarasimha, Karthikeyan Damodharan, and Sivanathan Chandramohan

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1 Introduction

A fistula is an abnormal connection between hollow viscus organs with epithelialized surfaces, such as the alimentary tract or the genitourinary tract, or between hollow viscus with a fluid cavity, as seen in abscess–fistula complexes. Fistulas are named based on the direction of which the contents flow; for example, with an enterocutaneous fistula, intestinal contents drained through the skin via an abnormal sinus tract. Fistulas have many causes, including iatrogenic, postoperative, or radiation-induced, or can arise de novo as seen from chronic inflammation or direct tumor invasion from locally advanced malignancies (Taggarshe et al. 2010; Pickhardt et al. 2002; Berry and Fischer 1996).

Fistula disease can be a debilitating chronic condition. Abnormal fistulae allow for contamination of usual sterile spaces, which can result in recurrent infections, requiring frequent emergency room visits and prolonged hospitalization.

K. A. Lee · N. Venkatanarasimha · K. Damodharan
S. Chandramohan (✉)
Department of Vascular and Interventional Radiology, Singapore General Hospital, Singapore, Singapore
e-mail: sivanathan.chandramohan@singhealth.com.sg

© Springer Nature Switzerland AG 2021

P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*, Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_29

Management of clinical symptoms, including chronic cutaneous wounds, persistent abnormal feculent drainage, can be taxing and greatly impacts patients' quality of life (Kaushal and Carlson 2004; Teieira et al. 2009; Cohen et al. 2008). This is particularly distressing for terminally ill patients with limited treatment options.

Management of fistulae remains a complex clinical problem, which requires a multidisciplinary approach including surgeons, gastroenterologists interventional radiology, wound care specialists, oncologists, and palliative care specialists. This chapter aims to provide a brief overview of an interventional radiologist's role in management and palliation of chronic fistulas.

2 Abscess–Fistula Complex

Abscess–fistula complex refers to intra-abdominal abscesses caused by abnormal fistulous tract. These collections can result from abnormal fistulae from the biliary system, the pancreatic duct, the bowel, or urinary system. Most common abscess–fistula complexes are caused by enteric fistulas from either the small or large bowel (Lee and Stein 2010). Approximately 44% of enteric fistulas are associated with intra-abdominal abscesses (Kerlan Jr et al. 1985). While a majority of cases are iatrogenic or post-operative in nature, others can arise de novo from acute infection, inflammatory bowel disease, or advanced ulcerating malignancies. The resolution of abscess and fistula healing depend largely on the inciting disease and the anatomy of the fistula. In patients with advanced malignancies, many with history of prior surgeries or radiation, who are immunosuppressed and often in a constant state of catabolism, these fistulous tracts may take far longer to heal or may never resolve.

The principle of management is essentially the same for all abscess–fistula complex (Ballard et al. 2015). It requires (1) drainage of the abscess collection, (2) proximal diversion, and/or (3) selective cannulation of the fistulae to allow for closure of the fistulous tract. The concern for abnormal fistulous connection to abscess cavity is raised when the drainage output from the abscess is greater than 100 mL or if there is a sudden increase of output post-abscess drainage. Few fistulas are identified on the initial placement of drainage catheter. Following decompression of the abscess, an abscessogram can be performed under fluoroscopy to interrogate and delineate the fistulous tract. For enteric fistulas, patients are managed with bowel rest and proximal diversion, usually via a nasogastric tube. Upon decompression of the abscess, the catheter tip should be placed close to the fistula effluent. In some cases, such as high output fistula, selective cannulation of the fistula tract is performed. A second small caliber drainage catheter is placed through the tract into the enteric system for 10–14 days to allow for the tract to mature. This catheter would then be sequentially retracted to allow for the closure of the fistula tract. The abscess drainage catheter remains in situ with fluoroscopic evaluation performed at 10–14 days or when output <20 mL to evaluate for adequate evacuation of the abscess cavity and closure of the fistulous tract. The clinical success is reported to be as high as 82% though the success rate is variable based on the patient population and nature of the abscess–fistula complex (Ballard et al. 2015; Papanicolaou et al. 1982; Laberge et al. 1992; D'Harcour et al. 1996).

3 Fistula of the Gastrointestinal Tract

Gastrointestinal (GI) fistulas can be classified based on their anatomy and output (Se et al. 2008). Anatomical classification divides the fistulas into external fistulas, referring to abnormal fistulation to from any local of the GI tract to the skin and internal fistulas, referring to abnormal fistulization from the GI tract to another organ, intraperitoneal space, retroperitoneal space, thorax, or the mediastinum. Enteric fistulas can also be classified based on output. Low output fistulas generally drain <200 mL over 24 h, and likely originates from the large bowel. Medium output fistulas and high output fistulas drains 200–500 mL and >500 mL over 24 h, respectively (Ballard et al. 2015). Medium- or high output fis-

tulas are usually associated with small bowel and can be associated with electrolyte imbalance from excessive fluid losses. Treatment approach can be different depending on anatomy or volume of output. This section will focus on enteric fistulas encountered in the management and palliation of oncology patients.

3.1 Enterocutaneous Fistula

Enterocutaneous fistula (ECF) is associated with a reported mortality of 10–30%. Approximately 85% of ECF are iatrogenic or postoperative in nature, as a result of unintended enterostomies during surgery, endoscopic or minimally invasive procedures, with a minority from inflammatory bowel disease, advanced ulcerating tumors or from penetrating trauma (Evenson and Fischer 2006; Draus Jr et al. 2006). The definitive management is surgery with resection and primary anastomosis. Thirty percent of the ECF spontaneously heals without intervention, while success in non-surgical management is observed up to 65% (Schein 2008). Unfortunately, patients with advanced malignancy or intractable fistulizing Crohn's disease are often poor surgical candidates. Furthermore, some of these patients have undergone extensive abdominal surgeries, chemotherapy, or radiation, such that these fistulas can be complex in nature. When referred to interventional radiology, these patients likely have failed prior conservative management.

There are multiple factors that implicate the closure of the fistula. ECF of esophageal origin has shorter spontaneous closure time. Gastric and small bowel ECF are less likely to close spontaneously due to the acidic drainage of gastric juices, and the likely high output drainage from the small bowel (Se et al. 2008). Single, long, and narrow tracts (>2 cm in length) are more likely to close than multiple, short, wide neck fistulas (enteric defect >1 cm). ECF with extensive skin breakdown and abdominal wall disruption are also difficult to heal (Se et al. 2008).

Reports have described various methods of percutaneous closure methods with variable success. Prior to any attempts for percutaneous closure, it is prudent to medically optimize the patient.

As previously discussed, 44% of enteric fistulas are associated with intra-abdominal abscess and prompt decompression of the abscess is warranted. Active infection and sepsis generate persistent catabolic states such that wound healing is significantly impaired. Furthermore, persistent purulent drainage through the sinus tract causes local inflammation and skin breakdown, which results in granulation tissue and fibrosis of the skin tract. The percutaneous access site selected for drainage should be healthy to avoid further skin and tissue damage (Rahman and Stavas 2015).

Total parenteral nutrition (TPN) is sometimes necessary during long duration of bowel rest and proximal diversion. TPN has been associated with decrease fistula output but did not affect closure times or mortality. It should be noted that TPN is also associated with various risk (Bierier and Hedrick 2010). Enteral feeding via a direct jejunostomy tube downstream from the fistula can also be performed percutaneously under fluoroscopic and ultrasound guidance. Octreotide somatostatin analogs have been used to decrease gut motility, suppress hormone release, and decrease mucus secretions. Reports have demonstrated decrease in fistula output and shortened closure time but did not affect overall closure rates (Stevens and Delicata 2011; Rahbour et al. 2012).

Involvement of wound care specialists is crucial in managing the skin site to prevent further wound breakdown. With advances in the wound vacuum methods, this can be used in conjunction with percutaneous methods to improve outcomes.

Small case series have shown effectiveness of percutaneous ECF closure device (Taggarshe et al. 2010; Draus Jr et al. 2006; Avalos-Gonzalez et al. 2010; CambjSpanuar et al. 2012; Lyon et al. 2013). However, in more chronic fistulas with complex anatomy, ECF closure device often fail on initial attempt and repeated procedures may be necessary. Antibiotics with sufficient Gram-negative coverage for gut flora should be given in preparation for tract closure.

A fluoroscopic sinogram is first obtained by cannulating the skin tract to best delineate the configuration of the fistula. The sinus tract should then be debrided and sanitized (Rahman and Stavas 2015). The debridement of the sinus tract allows removal of the granulation tissue and fibrous scarring along the tract, which promotes healing. This can be accomplished by percutaneous devices that score the tract. The use of the brush from the anal fistula plug device (Cook; Bloomington, Indiana, USA), Trerotola device (Arrow; Redding, Pennsylvania, USA), endoscopic brushes or forceps have been described. The tract is then irrigated slowly by infusing hydrogen peroxide along the tract (Rahman and Stavas 2015).

Once the tract is prepared, various closure materials can be used, including bioadhesives and extracellular matrix. Bioadhesives include fibrin glue or sealant, which could be injected along the sinus tract (Avalos-Gonzalez et al. 2010; CambjSpanuar et al. 2012; Lyon et al. 2013; Rabago et al. 2002). Once access of the ECF is obtained, the tip of the catheter or applicator is placed just outside the enterotomy. The glue or sealant is slowly injected while the catheter is pulled back. Extracellular matrix (ECM) is a biological scaffold of proteoglycan and non-proteoglycan material, which can be introduced via a sheath. ECM is pre-loaded on the sheath, and once the sheath is positioned appropriately in the sinus tract, the ECM can be pushed out using the stylet or introducer of the sheath. There are various materials available on the market; however, no direct comparison of the materials has been done.

The biodesign fistula plug (Cook; Bloomington, Indiana, USA) consists of (1) a radiopaque flange for securement at the enterotomy site, (2) the biodesign graft, and (3) a molnar disk for the cutaneous site. The biodesign graft is a non-cross-linked and non-dermis-based biologic graft, available in 4 mm or 7 mm width and 18 cm in length. This can be inserted percutaneously with a sheath and a pusher provided with the kit (Lyon et al. 2013).

More recently, laser ablation to facilitate complex, chronic ECF has been described for patients who have failed multiple prior attempts of ECF closure. Laser ablation has been described in closure of anal fistulas (Srinivasa et al. 2018). However, the use of laser ablation in ECF closure has only been reported in few select cases (Srinivasa et al. 2018).

3.2 Esophagorespiratory Fistula

Esophagorespiratory fistula (ERF) refers to an abnormal fistulous connection between the esophagus and the respiratory tract, a devastating complication from esophageal malignancy, with a reported incidence of 5–15% (Shin et al. 2004). ERF can also be seen in bronchogenic carcinoma in <1% of all presentation (Shin et al. 2004). ERF can occur as a sequelae of direct tumor invasion, preexisting stents, or perforation from laser treatment (4–6%) and plastic endoprotheses (5–8%). It can also occur during or after initiation of chemotherapy and radiation therapy (Katabathina et al. 2013). To date, there is no conclusive evidence that chemotherapy or radiation is associated with increased risk of perforation or fistula formation. However, it is noted to occur usually 6 weeks after initiation of treatment (Chen et al. 2014). Additional risk factors, such as T4 disease, extracapsular nodal disease, and re-radiation, are found to be associated with higher risk of perforation during or after radiation therapy. ERF is more likely to develop in patients of younger age, with cancers involving the middle third of the esophagus, and with poorly differentiated and necrotizing cancers penetrating the airway (Chen et al. 2014). ERF is associated with high mortality from pulmonary sepsis and severe intrathoracic infection, where prompt treatment is paramount. Without treatment, median survival is about 1 month.

Most common type of ERF is esophagotracheal fistula (52–57%), followed by esophagobronchial fistula (37–40%), and lastly esophagopulmonary fistula (3–11%), with fistulous communication with the lung parenchyma (Shin et al. 2010). Esophagopleural fistulas are rare and associated with very poor survival (Shin et al. 2010).

In the last two decades, placement of covered self-expandable metallic stent (SEMS) has been used to palliate malignant esophagorespiratory fistulas with reported treatment success of 67–100% (Shin et al. 2004; Saxon et al. 1995; Van Heel et al. 2010; Herth et al. 2010; Kim et al. 2018). There are various metallic stents available on the market, such as Wallflex stent and Ultraflex stent (Boston Scientific, Galway, Ireland), Niti-S (Taewoong Medical Co, Ltd., Gimpo-Si, Korea). These stents come in varying diameter and lengths and most are made of nitinol or similarly flexible material (Kulkarni et al. 2011). These stents can be used for various indications. Some stents (Dostent, MI Tech, Korea; Gianturco-Rosch Z-stent, Cook, Denmark) have anti-reflux valves and some stents have retrievable design (Choo stent, MI Tech, Korea; Song stent, Sooho Medical, Korea; FerX-ella, Ella CS, Czech Republic).

Understanding the fistula anatomy is crucial in determining the appropriate location of stent positioning. Stenting above the upper esophageal sphincter should be avoided as it is associated with pain, increased incidence of aspiration pneumonia, and increased risk of stent migration. In addition, the decision of placing an esophageal stent or an airway stent should be based on the configuration of the fistula. For patients with concurrent esophageal stricture and ERF, and minimal to mild airway stricture, an esophageal stent can treat both the stricture and the fistula (Shin et al. 2010). In patients with prior esophageal surgery, such as Ivor Lewis esophagectomy, previously placed esophageal stent, or ERF secondary to pressure-induced necrosis from prior esophageal stent, an airway stent should be considered (Shin et al. 2010). In patients with moderate to severe airway stricture and in patients with mild to no esophageal narrowing, an airway stent again should be considered, as the lack of esophageal stricture allows for migration and movement of the esophageal stent (Shin et al. 2010). Finally, in instances of concurrent moderate to severe airway and esophageal strictures, placement of both trachea and esophageal stents should be considered. This should be performed in concert with respiratory physician and the airway stent should first be placed to avoid worsening dyspnea associated with placement of esophageal stent. These patients should undergo very close monitoring as mechanical friction between the stents can cause pressure necrosis of the interposed tissue, resulting in catastrophic complications and fatal hemorrhage.

Like for stenting of any portion of the GI tract, the location and length of the defect/fistula should be well delineated prior procedure. For esophageal stenting, the patient is sedated and placed in the decubitus position. A 5 Fr angiographic catheter and hydrophilic glidewire are used to access the esophagus under fluoroscopic guidance. As the glidewire is advanced pass the defect, the glidewire is then exchanged for a 0.035 or 0.038 superstiff guidewire to allow for support for subsequent deployment of the stent. The stent is loaded onto the guidewire and advanced over the area of defect. Different stents may have different deployment mechanism, but most require uncovering the stent by pulling back the sheath. Forward tension is maintained on the delivery system to allow for deployment of the stent over the appropriate position. Esophagogram is performed at the conclusion of the stent deployment and the subsequent follow-up to evaluate for appropriate seal.

In larger series reports, successful fistula closure on initial attempt ranged from 77 to 80% (Shin et al. 2004; Kim et al. 2018; Balazs et al. 2008). Among the patients with initial clinical success, 35–37% experienced recurrent aspiration and symptoms of fistula reopening on subsequent follow-up (Shin et al. 2004; Kim et al. 2018). Etiology of reopening or recurrent symptoms includes tumor ingrowth or overgrowth, food impaction resulting in incomplete seal, stent migration, and stent covering disruption. In one study, upper esophageal stricture is an independent predictor of initial clinical failure and initial clinical failure is associated with shorter survival (Kim et al. 2018). Median survival ranged from 1.7 to 3.4 months, compared to median survival of 1.1–1.3 months with no treatment and best supportive care (Shin et al. 2004; Kim et al. 2018; Balazs et al. 2008). Major complications were

reported 6–33% of the cases. The reported rate of stent migration varies from 10 to 30% depending on the type of stent used. Airway compression and hemorrhage are noted in less than 10% of cases (Shin et al. 2004; Kim et al. 2018; Balazs et al. 2008).

3.3 Enterovesical Fistula

Enterovesical fistulas (EVF) are uncommon but associated with significant morbidity, with patients presenting with pneumaturia and fecaluria most commonly (Golabek et al. 2013). Most are reported as a complication of diverticular disease. The second most common etiology is malignancy, in advanced stage colon cancer and locally invasive bladder cancer. EVF are also seen as a rare complication of pelvic radiation and can have a delayed presentation, many years following initial treatment.

Enterovesical fistulas are classified as (1) colovesical, (2) rectovesical, (3) ileovesical, and (4) appendivesical; colovesical fistula is the most common, usually occurs between the sigmoid colon and the bladder dome (Golabek et al. 2013).

Surgical resection and diverting ostomy remain the gold standard of treatment. Non-surgical measures include bowel rest, TPN, and chronic suppressive antibiotics. Ultimately, a diverting stoma is necessary for definitive management. For patients with malignant fistulas, resection or defunctioning stomas sometimes cannot be safely performed due to advanced disease, comorbid condition, poor functional and nutritional status. For select patients, palliative stenting can be performed to managed symptoms and improve quality of life (Golabek et al. 2013; Ahmad et al. 2010). Colonic stenting has been increasingly used to relieve acute colonic obstruction as a bridge to surgery or for patients unfit for surgical intervention (Watt et al. 2007). Stenting for palliation of EVF has been reported in limited studies. Covered, self-expandable metallic stents (SEMS) are used to create a barrier between the fistulized bowel and bladder (Ahmad et al. 2010).

4 Fistula of the Genitourinary Tract

Genitourinary (GU) fistulas can be seen in locally advanced pelvic malignancies, such as cervical carcinoma or colorectal cancer, or following extensive pelvic operations and radiation therapy. Clinical symptoms are often devastating. Persistent urine drainage in vesicovaginal fistulas and feculent drainage from colovaginal fistulas are distressing and significantly limit quality of life. Unfortunately, most terminally ill patients are unable to tolerate surgical repair or diversion and are managed with best support care. This section will review more commonly encountered GU fistulas in a palliative care setting and discuss various novel techniques in symptom management.

4.1 Fistulas in Gynecologic Malignancies

Vesicovaginal and enterovaginal fistulas are most common fistulas encountered in gynecological malignancy, particularly in cervical cancer (Yu et al. 2004; Narayanan et al. 2009). FIGO stage IV cervical cancer denotes bladder and/or rectal invasion, such that urinary or colon fistulas are sequelae of locally invasive disease (Gerber and Schoenberg 1993). Combined chemotherapy and radiation is the treatment of choice of FIGO stage IIB or above cervical cancer, where some patients receive external beam radiation or vaginal vault brachytherapy. Radiation treatment can lead to progressive endarteritis obliterans, which leads to mucosa breakdown and necrosis. The incidence of vaginal fistulas following radiation in cervical cancer is reported to range from 1 to 5% (Papadopoulou et al. 2016).

As with other forms of fistulas, vesicovaginal and enterovaginal fistulas can be classified into (1) simple fistulas, involving single tract, defect size <0.5 cm, in non-irradiated tissue, and (2) complex fistulas with multiple tracts, wide-mouthed defects in irradiated or post-surgical field (Papadopoulou et al. 2016; VanBuren et al. 2018). Enterovaginal fistulas are also classified based on anatomy:

lower rectovaginal and high rectovaginal and colovaginal, which has implications in surgical management (VanBuren et al. 2018). In simple urinary fistulas, decompression with indwelling Foley catheter and urinary diversion with percutaneous nephrostomies may be sufficient to allow for spontaneous closure. However, in patients with larger or complex fistulas with multiple defects, surgical repair with resection, or surgical diversion are likely necessary.

For non-surgical candidates who have failed conservation management, some novel percutaneous techniques in small series have been reported for palliation and to optimize quality of life for these terminally ill patients (Knuttinen et al. 2015). Endoluminal stenting with kissing covered stents deployed in a transvaginal and transanal approach has been described in treatment of colovaginal fistulas, which has failed conservative management. In addition, small case series have reported the use of occluder device (Amplatz plug II; St. Jude Medical, Inc. St. Paul, Minnesota, USA) deployed via a transvaginal approach in management of colovaginal fistula (Knuttinen et al. 2015). Short-term follow-up noted significant improvement in symptoms without major complications.

4.2 Ureteroenteric Fistula

Ureteroenteric fistulas are rare, representing 1% of all urinary tract fistulas. Majority are sequelae of penetrating trauma or iatrogenic injury (Fig. 1), some can be seen in locally advanced pelvic malignancies, prior radiation, inflammatory bowel disease, and chronic renal transplant rejection (Lang et al. 2015). Surgical management, including ureteroneocystostomy, Boari flap with ureter reimplantation, uretero-ureterostomy, has a reported success rate of fistula closure up to 70% (Choi et al. 2010). Non-surgical management options, with percutaneous nephrostomies or double-J ureteral stents, or with long-term antibiotic therapy, are noted to facilitate fistula closure up to 62%. In addition, techniques of percutaneous ureteroneocystostomy have been described in patients with long ureteral dehiscence or large neoplastic mass obstructing pelvic ureter in small case series (Lang et al. 2015).

Fig. 1 A 65-year-old female with uretero enteric fistula managed by ureteric stenting. Nephrostogram immediately after ureteric stenting shows previously injected contrast pooled in the small bowel (short black arrow) and the site of fistulation (black arrow head). Please noted the contrast draining through the sideholes of ureteric stent into the bladder (long black arrow)

5 Fistula Related to Interventional Oncology Procedures

Local ablative therapy of soft tissue tumors continues to evolve over the past decade, now used for both palliative and curative intent. In

very rare circumstances, abnormal fistulous communication can occur secondary to collateral thermal damage caused along the ablation tract.

5.1 Bronchopleural Fistula

Bronchopleural fistulas (BPF) from thermal ablation of pulmonary lesions are very rare. In a recent report reviewing 1403 lung tumors, treated in 1000 radiofrequency ablations (RFA) sessions in 420 consecutive patients, bronchopleural fistulas were reported in four cases (0.4%) (Kashima et al. 2011). BPF are classified based on location: (1) central, denoting pleural communication with trachea or segmental bronchi, and (2) peripheral, denoting pleural communication with peripheral bronchi (Gaur et al. 2014). Most cases of BPF associated with ablations are peripheral in nature with nodules in close proximity or abutting the pleural. BPF usually presents 8–12 days post procedure. Surgical closure is usually required. Some case series have reported targeting the lucent BPF tract under computer tomographic guidance and tract occlusion with silicone embolic material or N-Butyl cyanoacrylate (NBCA) glue (Powell and Baum 2018) (Fig. 2).

5.2 Enteric and Biliary Fistulas

The overall mortality and major complication rates are low in local ablative therapy of primary liver tumor and liver metastases, with mortality rates up to 1.4% and major complications occurring 2.2–5.7% (Kim and Thomas 2014). Similarly, major complication rates from thermal ablation of renal tumors are low, with a reported incidence of 2–6% (Kim and Thomas 2014). Abnormal fistulous communication resulting from thermal ablation is extremely rare (<1%) and are only described as case reports in the literature.

Enteric fistulas from liver or renal ablation usually results from thermal injury of adjacent colon. Stomach and small bowel are more resistant thermal injury owing to the thicker walls and peristalsis. Colon is relatively thin-walled and are usually fixed in location; thus, without appropriate thermal protection with displacement, colon injury can occur. This often necessitates percutaneous drainage and surgical repair.

Biliary fistulas to adjacent vasculature and along the ablation trajectory have also been reported. Bronchobiliary fistulas have been reported in post-liver ablation patients presenting with severe pneumonia and biliptysis (Kim et al. 2005). In reported cases of bronchobiliary fistulas, target lesions are often close to the liver dome and diaphragmatic injury are often implicated.

6 Conclusion

In summary, fistula disease can result in high morbidity and mortality. Contamination of usual sterile spaces can result in difficult to management infections, such as those seen in abscess–fistula complexes and various enteric fistulas. In certain cases, fistulization can result in fatal infection if not address promptly. Chronic fistula disease also significantly impairs patients' quality of life. In percutaneous management of all fistula diseases, the etiology, anatomy, and configuration of the fistulas have to be well studied to allow for selection of optimal closure or diversion techniques. Furthermore, due to the inherent complexity of the disease, a multidisciplinary approach in management is paramount.

Fig. 2 A 75-year-old man with metastatic colorectal adenocarcinoma, presenting with a solitary pulmonary metastasis in the left lower lobe, status post-microwave ablation. Three days following ablation, patient presents with persistent left pneumothorax despite chest drainage. (Image Courtesy Dr.Too Chow Wei). (**a**) Axial computer tomographic (CT) image of the chest demonstrated a large left pneumothorax (long white arrow) with subcutaneous emphysema despite indwelling chest tube (arrowhead). A lucent tract in the ablation zone (arrow) extended to the pleura, consistent with a bronchopulmonary fistula. (**b**) The tract is targeted under CT fluoroscopy guidance with a 22 Chiba needle (white arrow). (**c**) The tract is embolized by injecting a 1:1 mixture of Lipiodol:NBCA (white arrow). (**d**) Axial CT of the chest 11 days following embolization demonstrates full re-expansion of the left lung with the glue case (white arrow)

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Intrathecal Pain Pumps: Placement and Management

Douglas P. Beall, Dereck D. Wagoner, Edward S. Yoon, Brooks M. Koenig, Jennifer Witherby, Michael E. Flamm, Adrea S. Knoll, Andrew W. Favre, Greg Pace, Elizabeth Bolen, Madelyn Nordgren, and Todd Russell

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D. P. Beall (✉) · D. D. Wagoner
B. M. Koenig · J. Witherby · A. S. Knoll
Oklahoma City, OK, USA
e-mail: db@clinrad.org; jw@clinrad.org

E. S. Yoon
Hospital for Special Surgery, New York, NY, USA
e-mail: yoone@hss.edu

M. E. Flamm
Brooklyn, NY, USA

A. W. Favre
Lakewood Ranch, FL, USA

G. Pace · E. Bolen · M. Nordgren · T. Russell
Edmond, OK, USA
e-mail: greg.h.pace@medtronic.com; elizabeth.a.bolen@medtronic.com; Madelyn.n.nordgren@medtronic.com; todd.e.russell@medtronic.com

© Springer Nature Switzerland AG 2021

P. L. Munk, S. B Babu (eds.), *Interventional Radiology in Palliative Care*,
Medical Radiology Diagnostic Imaging, https://doi.org/10.1007/978-3-030-65463-4_30

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Abstract

Intrathecal drug delivery has expanded since the inception of this technology in the 1980s and is utilized for a number of different conditions including pain control and management of spasticity. The use of intrathecal pumps is less common than most other techniques for interventional pain management but is essential in such conditions as refractory pain, cancer pain, multifocal pain, severe spasticity, and in patients who are not candidates for surgical correction of their underlying condition. Intrathecal drug delivery is usually considered when analgesics or antispasmodics administered via the oral, transdermal, or intravenous routes are ineffective or are associated with unacceptable side effects. The intrathecal delivery of medications bypasses the blood–brain barrier, which produces much higher concentrations of medication within the cerebrospinal fluid. This higher concentration can serve to dramatically reduce the effective dose of the medication and can be associated with higher rates of pain and spasm reduction compared to other routes of medication delivery. Although intrathecal drug delivery has been shown to be effective and cost-effective this less utilized pain management tool is less well understood regarding its implantation and management than other technologies. This chapter will serve to highlight the proper clinical use and appropriate management of intrathecal pumps for the management of spasticity and pain.

Abbreviations

AE	Adverse event
BBB	Blood–brain barrier
CAP	Catheter aspiration port
CDC	Center for Disease Control
CME	Continuing medical education
CMM	Conventional medical management
CP	Cerebral palsy
CSF	Cerebrospinal fluid
CT	Computed tomography
CVA	Cerebrovascular accident
CYP	Cytochrome P450
FDA	Food and drug administration
GI	Gastrointestinal
ITB	Intrathecal baclofen
MAS	Modified Ashworth scale
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
myPTM™	Personal therapy manager
OIH	Opioid-induced hyperalgesia
PACC	Polyanalgesic Concensus Conference
PSS	Post-stroke spasticity
RCT	Randomized control trial
ROM	Range of movement
SCI	Spinal cord injury
SCS	Spinal cord stimulation
SCS	Spinal cord stimulator
TBI	Traumatic brain injury
TDD	Targeted drug delivery

1 Introduction and Background for Intrathecal Pumps Used for Pain and Spasticity

1.1 Intrathecal Drug Delivery for Pain

Chronic pain is exceedingly common with prevalence estimates ranging from 13 to 51% and is more common than other chronic conditions such as diabetes and more common than diabetes, cancer, and heart disease combined (Breivik et al. 2006; Bridges 2012; Fayaz et al. 2016; Manchikanti et al. 2009; Gupta et al. 2010; Moody 2012; Tsang et al. 2008). There are more than 100 million Americans suffering from chronic pain and estimates from the Institute of Medicine place the annual healthcare cost of treating this pain at nearly $635 billion annually (Relieving Pain in America 2011).

In addition to the economic costs, chronic pain is a significant burden causing significant reduction in patients' quality of life. A national pain audit found that the average quality of life score in people suffering from chronic pain was lower than that reported by people suffering from progressive neurological disorders such as Parkinson's disease (Price et al. 2012). Common chronic pain disorders such as migraine headaches and neck pain cause significant disruptions in quality of life and low back pain causes more disability worldwide than any other single condition (Hoy et al. 2014). Patients suffering from chronic pain are also less productive in their work and are seven times more likely to quit their jobs due to ill health than the general population (Donaldson 2009).

The management strategies of chronic pain typically run the gamut beginning with the most conservative and least invasive progressing to treatment options that are more definitive but that may be associated with higher risk and a greater amount of invasiveness (Krames and Olson 1997). The overarching approach is to stop with the combination of the least invasive treatment that provides substantive relief for the patient. A concept of this continuum of treatment was introduced by Stamatos et al. when the authors proposed a pain treatment ladder focusing on the specific area of the body that hurts rather than treating the entire body (Fig. 1) (Stamatos et al.

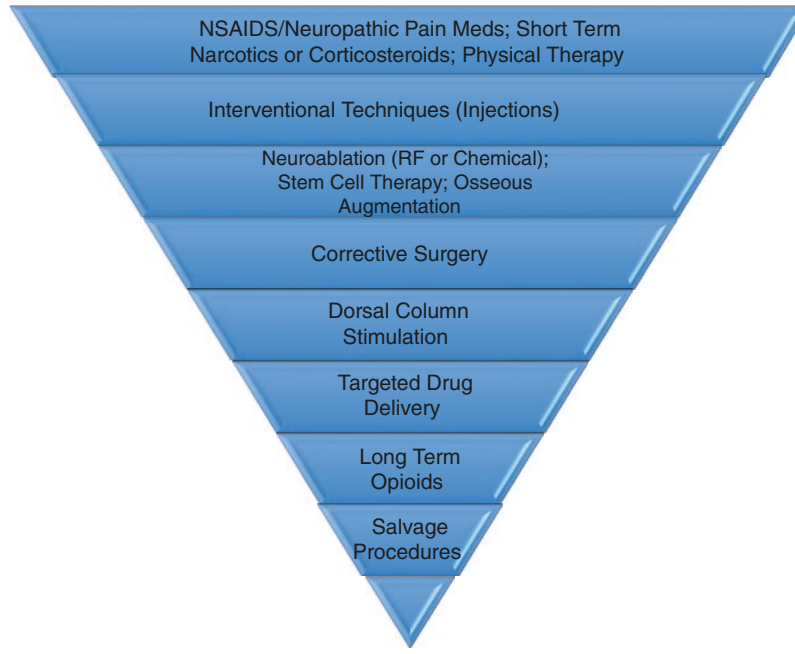

Fig. 1 The Stamatos version of the pain treatment ladder or inverse pyramid proposes focusing on the area of the body causing the pain, rather than initiating systemic treatment. In contrast to the systemic treatment, interventional therapies, corrective surgery, neurostimulation and targeted drug delivery are placed before long-term opioid therapy. This allows targeting of medication or therapy to the specific area of pain before a more general pain treatment approach is applied

2005). This ladder or inverse pyramid begins with non-narcotic medications, corticosteroids, and physical therapy and focuses on the area of the body causing the pain, rather than initiating systemic treatment. As opposed to systemic treatment, interventional therapies, corrective surgery, neuromodulation and targeted drug delivery are recommended prior to initiating long-term opioid therapy. This allows targeting of medication or therapy to the specific area of pain before a more general pain treatment approach is applied. As we have seen the great amount of morbidity and mortality associated with the opioid epidemic this treatment approach is now recognized as a much safer and more effective approach (Nelson et al. 2015).

Traditionally, Spinal Cord Stimulation (SCS) and Targeted Drug Delivery (TDD) were thought of as options of last resort and something to be made available to patients after other methods of treating pain have failed (Duarte et al. 2012; Sparkes et al. 2015; Mann et al. 2015). The medical management of chronic pain by using prescription opioids can be complicated by inadequate analgesia, addiction, rapid dose escalation, intolerant side effects, opioid-induced hyperalgesia, and overdose (Mann et al. 2015; Noble et al. 2008; International Association for the Study of Pain 2007; Angst and Clark 2006a; CDC 2011), but opioid medications were traditionally used prior to SCS and TDD and were commonly referred to as "conservative treatment." The treatment regimen has been influenced by the opioid epidemic and the increased number of deaths associated with narcotic-induced respiratory suppression (Boslett et al. 2019). The sixfold increased rate of death due to opioid overdose seen from 1999 to 2017 served to emphasize the need alternate therapies to oral or transdermal opioids for chronic non-malignant pain (Boslett et al. 2019).

The Food and Drug Administration (FDA) approved a concentrated form of morphine (Infumorph® Sterile Solution, Baxter Healthcare Corp., Deerfield, IL, USA) in 1991 that was specifically developed for intrathecal use by using a continuous microinfusion device. The intrathecal delivery provides an alternate route of opioid administration. Rather than a systemic distribution of an opioid with activity on a wide array of systemic mu receptors, the TDD focuses the medication on the mu receptors present in the dorsal horn of the spinal cord. This specifically targets spinal mu receptors and is the reason that intrathecal medication delivery is known as Targeted Drug Delivery.

Targeted Drug Delivery has been successful in managing pain for patients with a variety of disorders including cancer, peripheral neuropathies, arachnoiditis, complex regional pain syndrome, spinal stenosis, and failed low back syndrome (Deer et al. 2010a). A critical point of emphasis that went in to developing an intrathecal drug delivery system was the assumption that the more effective delivery of the drug allowed for the elimination or near elimination of systemic medications like oral or transdermal opioids. This technique has been shown with Oxford Level 1 data to be more effective, less toxic, and to cause less mortality than Conventional Medical Management (CMM) (Fig. 2) (Smith et al. 2002; Staats et al. 2004).

The FDA-approved indications for TDD includes chronic epidural or intrathecal infusion of Infumorph® or Mitigo™ (preservative-free morphine sulfate sterile solution) for chronic intractable pain or Prialt® (ziconotide intrathecal infusion; Jazz Pharmaceuticals, Inc., Dublin, Ireland) for severe chronic pain. These indications are best employed prior to chronic oral or transdermal opioids given the increased safety of intrathecal use as compared to CMM (Fig. 2b, c) as well as the advantage in cost-effectiveness that TDD has over high cost CMM (Fig. 3) (Stearns et al. 2016). In addition to being safer and more cost-effective than CMM, the practitioner should also be aware that TDD is more effective than CMM (Fig. 2a) and the effectiveness of current medications to achieve sufficient relief of neuropathic and non-neuropathic pain is less than optimal with about one-third of patients receiving insufficient pain relief (Fig. 4).

If the patient on CMM is determined to be a good candidate for TDD with intrathecal pump

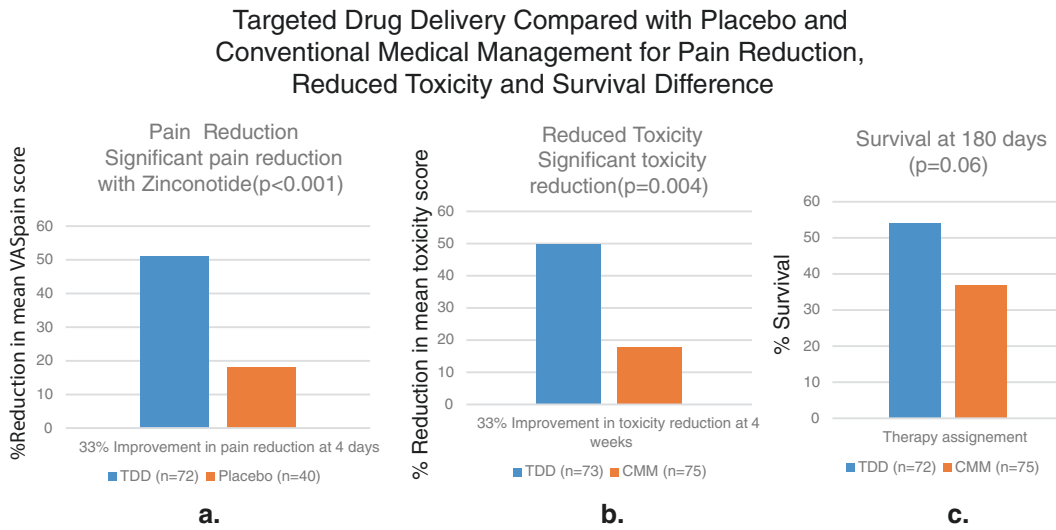

Fig. 2 (**a**–**c**) When comparing Targeted Drug Delivery (TDD) with placebo for pain reduction (bar graphs in **a**), TDD has a statistically significant improvement in pain reduction seen 4 days after initiation of therapy with 33% better pain reduction than the placebo. In a comparison of Targeted Drug Delivery (TDD) with Conventional Medical Management (CMM) for toxicity (bar graphs in b), the TDD showed a statistically significant reduction in toxicity with a 33% less toxicity than CMM at 4 weeks. When comparing Targeted Drug Delivery (TDD) with Conventional Medical Management (CMM) for survival or mortality difference, TDD had a 17% better survival rate than CMM at 180 days (bar graphs in **c**). This difference was not quite statistically significant but was extremely close to significance with a p value of 0.06. (1) Smith TJ, Staats PS, Deer T, Stearns LJ, et al. Randomized clinical trial of an implantable drug delivery (IDDS) system compared with comprehensive medical management (CMM) for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol*. 2002;20(19):4040–4049. (2) Staats PS, Yearwood T, Charapata SG, et al. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. *JAMA*: 2004;291(1):63–70

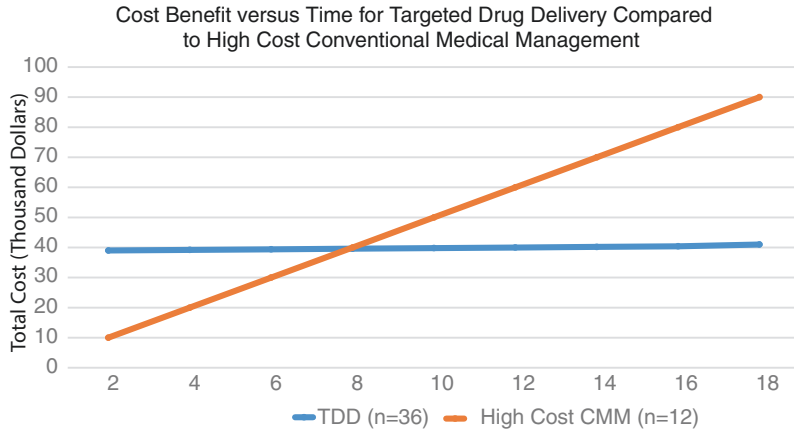

Fig. 3 Line graph showing the cost-effectiveness and cost-benefit of Targeted Drug Delivery (TDD) (solid orange line) shown in 36 patients as compared with high cost Conventional Medical Management (CMM) (solid blue line) in 12 patients. The crossover time point where the TDD began to show better cost-effectiveness than CMM was between 7 and 8 months

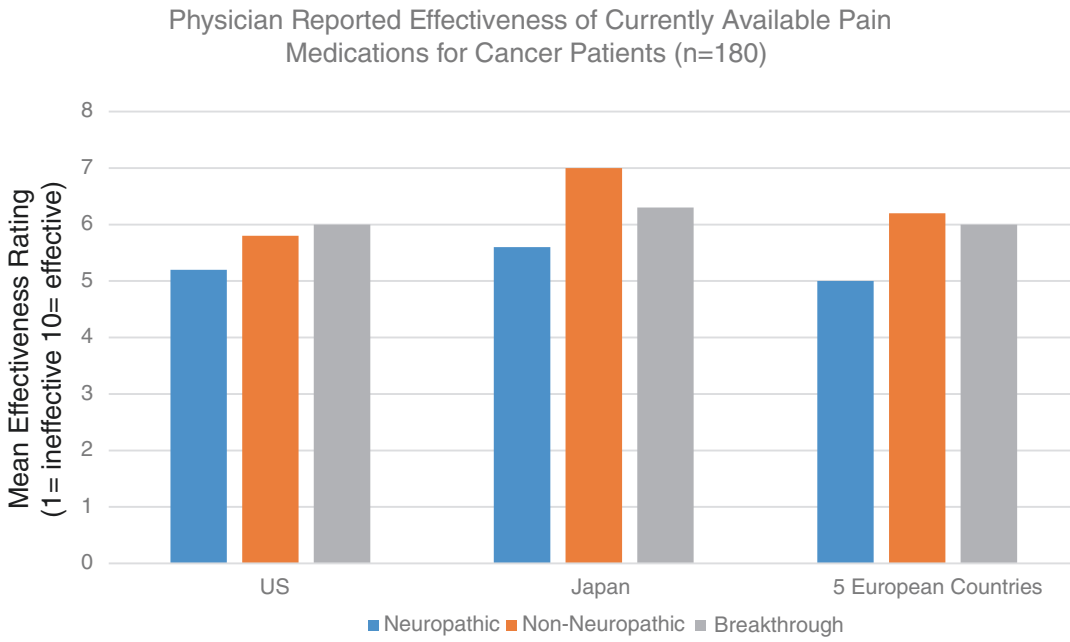

Fig. 4 Physical reported effectiveness of currently available pain medications for cancer patients in the United States, Japan and in five European countries shows the mean effectiveness to be less than optimally effective with approximately 30% of patients achieving insufficient pain relief. (1) DataMonitor. Stakeholder Insight: Cancer Pain. Published December 2009. Reference Code: DMHC2536

implantation and a number of other factors are present including a disease state that needs further treatment, an inadequate response to previous conservative management and the patient has demonstrated compliance with previous treatment regiments, they would be a candidate for an intrathecal drug trial if no contraindications exist (discussed in Sect. 3.1).

1.2 Intrathecal Drug Delivery for Spasticity

Spasticity is defined as an abnormal increase in muscle tone caused by injury of upper motor neuron pathways regulating muscles and may be caused by injury or disease of the central nervous system. There is a velocity-dependent increased resistance to passive stretch, and this may be characterized by exaggerated tendon jerks and accompanied by hyper-excitability of the stretch reflex (Emos and Agarwal 2018). A more encompassing definition is from the 2005 SPASM consortium which defines spasticity as disordered sensorimotor control resulting from an upper motor neuron lesion that presents as intermittent or sustained involuntary activation of muscles (Saulino et al. 2016)

There are more than half a million people in the United States and more than 12 million people worldwide are affected by spasticity (Stegmayr et al. 1997). The common etiologies of spasticity are divided into spasticity of spinal origin including spinal cord injury (SCI) and multiple sclerosis (MS) and spasticity of cerebral origin including post-stroke spasticity (PSS), traumatic brain injury (TBI), and cerebral palsy (CP).

Spasticity of spinal cord origin is most commonly seen in patients with, spinal cord disease, multiple sclerosis, or SCI. Spinal cord injury is often thought to be the result of a traumatic insult to the spinal column, but spinal cord injury can also result from disease affect-

ing the spinal cord. There are about 12,000 new cases of SCI that occur each year and in the last 20 years the majority of the injuries have resulted in incomplete tetraplegia (30.1%) and complete paraplegia (25.6%) (Anson and Shepherd 1996). It has been described previously that in a series of 348 patients with an SCI, 12% of the patients have severe spasticity that interferes with their activities of daily life while nearly two-third of the remaining patients have spasticity but not to the same degree where it interferes with their daily activities. When treating SCI patients for their spasticity, it should be known that the spasticity management does not interfere with the medical management for spinal cord injury.

Multiple sclerosis, literally translated, means many scars affect 1 million people in the United States and almost 2.5 million people worldwide (Multiple Sclerosis Council for Clinical Practice Guidelines 2003; Wallin et al. 2019). This disease process is an autoimmune condition where there may be activation of myelin-reactive T cells that express adhesion molecules that allow their entry through the blood–brain barrier (BBB) to attack the myelin cells that would otherwise be producing the fatty myelin that protects the neurons in the brain and spinal cord. The scarring that results from the autoimmune reaction forms plaques in the central nervous system (CNS) that block or slow down the neural impulses traveling within the CNS.

Movement varies greatly in patients with MS depending upon the location of the plaques within the brain and spinal cord and spasticity is a common feature of patients with MS with up to 84% experiencing some degree of spasticity (Wallin et al. 2019). There are 17% of patients who have spasticity that frequently affects their ability to perform daily activities and another 17% that have to modify their activities of daily life because of the spasticity (Rizzo et al. 2004a). As with SCI, the spasticity management of patients with MS does not interfere with the medical management of the MS.

Cerebrovascular accident (CVA) or stroke is common with an estimated 15 million people worldwide affected each year (Katan and Luft 2018). Of these, five million die and another five million are permanently disabled with 38% of those individuals experiencing post-stroke spasticity (PSS) (Watkins et al. 2002). Spasticity may occur promptly after a stroke and causes disability in about one-third of stroke patients within the first year (Watkins et al. 2002).

There are two primary types of stroke including ischemic stroke when the blood flow to the brain is interrupted and hemorrhagic stroke that results from a vessel that bleeds into the brain. Ischemic stroke accounts for approximately 80% of all strokes and results from thrombosis one of the cerebral vessels.

The PSS is thought to result from the stroke-related brain damage that prevents inhibitory signals from being sent to the spinal cord. The resulting imbalance of inhibitory and excitatory signals at the spinal level produces the spasticity. As with other sources of spasticity, the management of the spasticity does not interfere with the stroke medical management.

Another cerebral-related cause of spasticity is Traumatic Brain Injury (TBI). This is a disability that persists life-long after injury and contributes to an estimated 1.7 million deaths, hospitalizations, and emergency department visits per year (Thurman et al. 1999; Langlois et al. 2006). Nearly 20% of patients with TBI will experience spasticity and for those patients with injuries affecting the mid-brain the spasticity rate is over 50% (Wedekind and Lippert-Gruner 2005).

Substantial external physical force may produce enough neural dame to produce TBI that may result in a diminished or altered state of consciousness that can result in impaired cognitive abilities and decreased physical function. The spasticity that is often encountered results from lesions in upper motor neurons and although this mostly causes an adverse effect on physical movement, this can assist the patient in leg extension for walking or finger flexion for grasping. As with the other primary conditions that produce spasticity, the treatment for the spasticity and the benefit that this produces needs to be balanced against any potential downside to relieving the excess muscle tone.

Cerebral palsy (CP) is another relatively common cause of spasticity affecting about 800,000 children and adults in the United States with approximately 10,000 children developing CP each year (Rosenbaum et al. 2007; Christensen et al. 2014; Boyle et al. 2011). The condition of CP describes a somewhat heterogeneous group of disorders of brain development that causes difficulties in movement and posture. Although the condition is non-progressive, it causes spasticity in the majority of the patients and can significantly limit patient activity (Odding et al. 2006).

The functional impairments associated with the severe spasticity seen in all of these disease processes include pain, difficulty sleeping, flexion contractures, and bladder and bowel dysfunction (Dvorak et al. 2011; Rizzo et al. 2004b; Mutch et al. 1992; Shamsoddini et al. 2014; Mandigo and Anderson 2006). Patients with spasticity also have difficulty with various activities such as walking, changing positions, mobilizing from a wheelchair, and other activities of daily life (Dvorak et al. 2011; Rizzo et al. 2004b; Mutch et al. 1992; Shamsoddini et al. 2014; Mandigo and Anderson 2006). This very often results in adverse effects on their daily lives with decreased ability to work and social isolation. The definition of severe spasticity is not based on a grade or a scale but rather on the degree that it is troublesome or problematic to the patient or the caregivers.

The pathophysiology of spasticity is thought to be associated with an imbalance between descending excitatory and inhibitory impulses to the alpha motor neurons. There is an interruption of descending inhibitory nerve signals of the brain and spinal cord that produces the imbalance between excitation and inhibition (Trompetto et al. 2014). The motor neurons are divided into the upper and lower motor neurons. The upper motor neurons descend from the motor cortex of the brain to the spinal cord and some of these neurons carry inhibitory signals. The lower motor neurons are the pathway from the spinal cord to the muscle fibers. Damage to the upper motor neuron pathways such as the rubrospinal, reticulospinal, and vestibulospinal tracts can cause a lack of inhibition thereby causing spasticity. The damage and reduction of these inhibitory descending tracts removes the normal inhibition of the reflex arcs within the gray matter of the spinal cord giving rise to a hyperactive reflex arc and spasticity (Trompetto et al. 2014).

So in a patient with one of the conditions described above that produces severe spasticity and has had management of their spasticity that resulted in ineffective outcomes or intolerable side effects from oral baclofen, ITB may be considered as a treatment option in adult patients and pediatric patients age four and above. This option is nondestructive, adjustable and is reversible by pump explantation. Prior to pump implantation, a standard screening test is required to determine if ITB Therapy is appropriate for the patient (discussed in Sect. 3.1). This screening test allows the patient to try the therapy before committing to an implant.

2 The Components of Intrathecal Drug Delivery

2.1 SynchroMed II Intrathecal Pump

The SynchroMed II Intrathecal Pump (Fig. 5) is an implantable and programmable infusion pump. The on-label indications for the pump include use for chronic intraspinal (epidural and intrathecal) infusion of preservative-free morphine sulfate sterile solution in the treatment of chronic intractable pain. The indications also include chronic intrathecal infusion of preservative-free ziconotide sterile solution (Prialt®) for the management of severe chronic pain, and chronic intrathecal infusion of Lioresal® intrathecal baclofen injection for the management of severe spasticity.

The contraindications include the presence of infection, an implant depth greater than 2.5 cm below skin, insufficient body size, spinal anomalies precluding placement, drugs with preservatives, drug formulations with pH $\leq$3, and the use

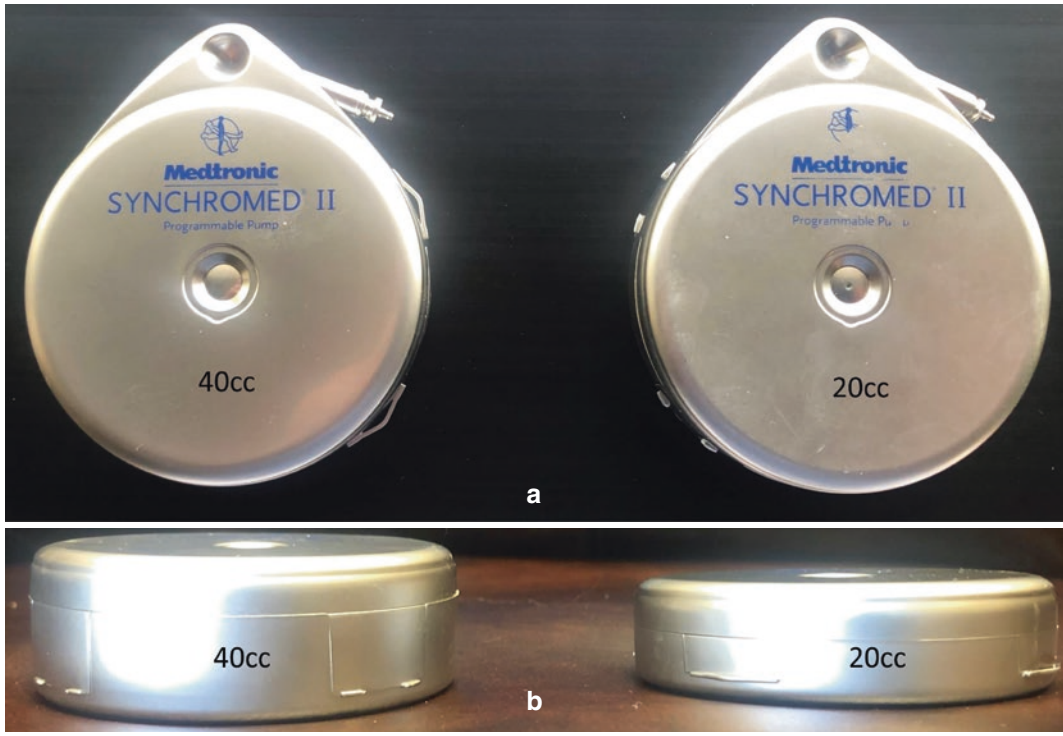

Fig. 5 The Medtronic SynchroMed II Intrathecal Pump is an implantable and programmable infusion pump that connects to a catheter that extends from the pump to the intrathecal space. The pump allows for a variety of different dose adjustments and titrations

of the Personal Therapy Manager to administer opioid to opioid-naïve patients or to administer ziconotide.

Importantly, the pump is Magnetic Resonance (MR) imaging conditionally safe at 1.5 T and 3.0 T and the medication does not have to be removed prior to having an MR imaging exam. This is important, as many patients who have the need for TDD will also have the need for an MR imaging exam at some point in their future. In patients that have a spinal cord stimulator (SCS), it was estimated that approximately 82% of those patients would need to have at least one MRI within 5 years of the implant (Desai et al. 2015). The need for additional MR imaging exams in patients undergoing TDD can be expected to be at least as high or higher as compared with patients with SCSs.

The SynchroMed II pump flow rate is highly adjustable and allows for dose adjustment and titration with flow rates as low as 0.048 mL and as high was 24 mL per day. There are four types of infusion modes. These modes are simple continuous, flex mode, minimum rate, and stopped mode. The different modes provide an extensive ability to perform fine dose adjustments and to optimize the dose for each individual patient.

The continuous rate is an infusion of a specified dose per day at a constant rate (Fig. 6). The flex mode or flex dosing allows independent doses to be delivered at different intervals throughout the day, with a fixed basal rate that is given between specified times (Fig. 7). Flex dosing is different from periodic blousing where one may give a series of bolus doses during the course of a day, with a low basal rate the remainder of the day. The flex dosing function helps to managing the patient's symptoms when their symptomatology predictably waxes and wanes during the course of the day. The minimum rate

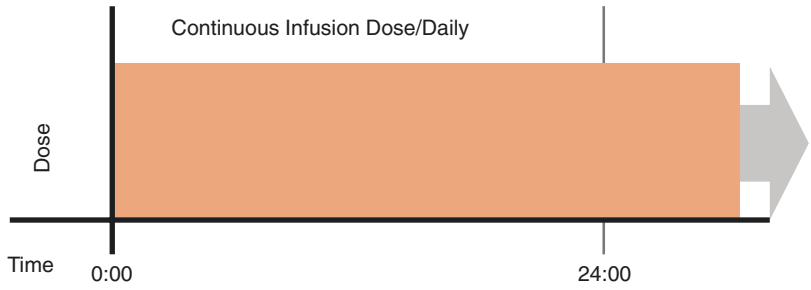

Fig. 6 The simple continuous infusion mode means that there is continuous infusion of a specified dose (indicated by the orange shaded area) per day at a constant rate

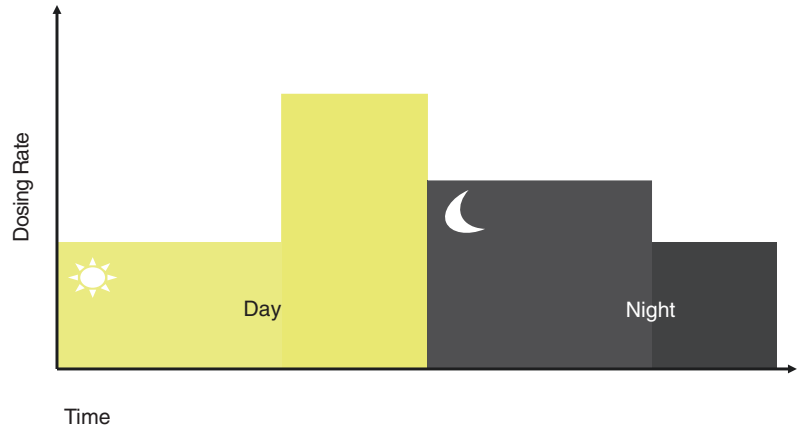

Fig. 7 Flex dosing allows separate doses to be delivered at different intervals throughout the day (yellow) and night (black), with a fixed basal rate to be delivered between the specified times

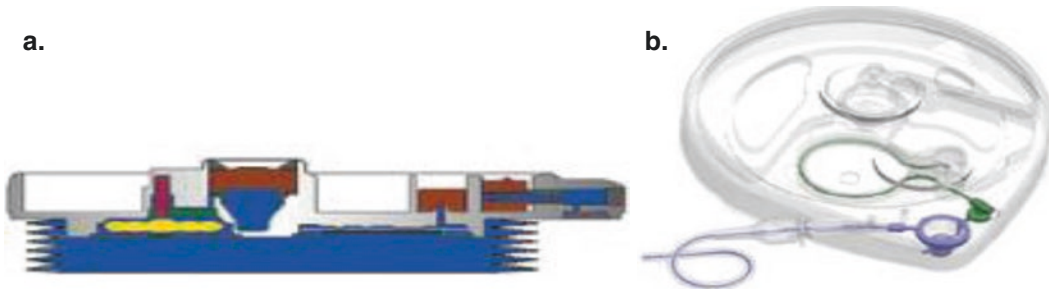

Fig. 8 The anatomy of the SynchroMed II Intrathecal Pump. The drug reservoir is located on the posterior portion of the pump (area shaded in blue in **a**). The internal catheter tubing (green shaded tubing in **b**) functions to carry the contents of the pump reservoir to the drug delivery catheter (purple shaded catheter in **b**) attached to the catheter port

is a continuous infusion at a rate of approximately 0.006 mL/day. This rate delivers a non-therapeutic dose of medication over the course of 24 h that is designed to maintain pump tubing patency until pump is restarted. If turned off completely, there is risk of damaging the internal pump tubing. The pump is shipped with saline in the reservoir and the setting turned to minimum rate mode. When the pump is in stopped mode, the rotor stops and the peristaltic motion that propels the fluid through the inner tubing is turned off. The pump will alarm after 48 h when the pump is in the stopped mode and to prevent damage to the internal tubing the pump should not be placed in the stop drug delivery for more than 48 h.

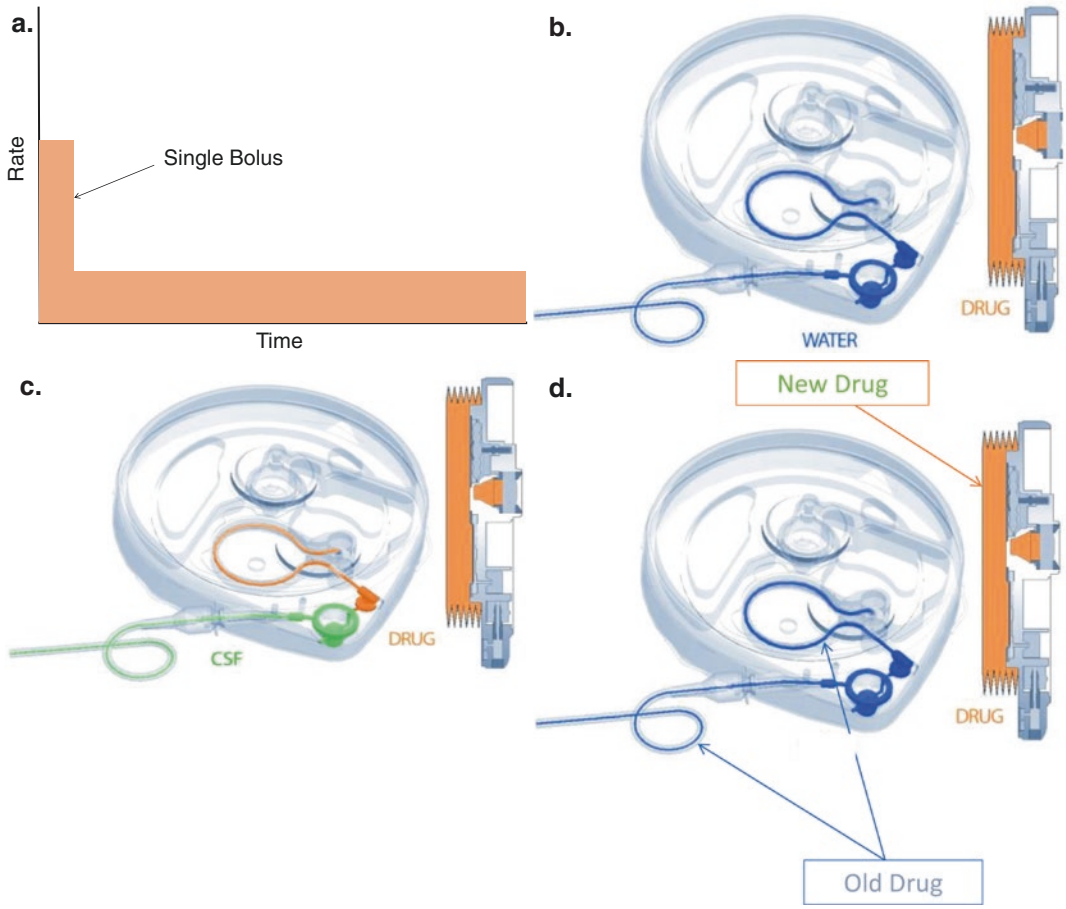

Fig. 9 (**a**–**d**) A single bolus dose delivers a specified dose over a specific programmed duration (**a**). A priming bolus pumps the drug from the reservoir (area indicated in orange in **b**) to the pump tubing (indicated by blue in **b** and orange in **a**) then from the pump tubing to the catheter (indicated by blue in **b** and green in **c**). The pump is shipped with saline which is then aspirated and filled with drug which is then bolused to the catheter tip which replaces the cerebrospinal fluid (CSF) which fills the catheter during placement of the catheter into the intrathecal space. A bridge bolus is used when changing the concentration or type of drug in the pump reservoir. The bridge bolus clears the old drug solution (indicated by blue in **d**) from the fluid pathway at the appropriate rate for the previous concentration. This prevents an under dose or overdose when converting from the old drug concentration (indicated by blue in **d**) to the new drug concentration (indicated by orange in **d**)

The pump's internal fluid reservoir has volumes of either 20 or 40 mL. The pumps are of identical diameters but the 40 mL pump has a larger reservoir (Figs. 5 and 8) making the larger volume pump thicker than the smaller pump. The decision about which pump to use relates to the drug dosage needed for treatment effect in each particular patient. The goal is to maximize the time between refills as much as possible to make it convenient for the patient while keeping in mind that the maximum time that the medication is allowed to remain in the pump is 6 months.

There are three primary bolus options that may be used in clinical practice including the single bolus, the priming bolus, and the bridge bolus (Fig. 9). Bolus dosing can be performed with either the simple continuous or the flex mode. Whenever a bolus is programmed into the

pump, it will be delivered immediately following the programming and, when complete, the pump will return to the previous programmed infusion mode. A single bolus can be given at any time deemed necessary by the managing clinician. The priming bolus is used to prime the pump tubing and catheter following an implant procedure or a catheter interrogation procedure. A bridge bolus is programmed when a drug or concentration change has been made during a pump refill.

A single bolus delivers a specified dose over a specific programmed duration (Fig. 9a) and is typically used for delivering a therapeutic bolus dose of drug or for troubleshooting in a case of suspected catheter malfunction. A priming bolus quickly fills empty pump tubing and the empty catheter (Fig. 9b, c). The priming bolus is used for priming the tubing and catheter during the initial pump implant or following pump and/or catheter revision surgery or during diagnostic procedures such as catheter interrogation with contrast.

A point of caution should be noted when performing priming boluses. The mixing of drug and non-drug fluids occurs at high flow rates that may be used during a priming bolus. This mixing can result in patients receiving drug prior to the end of the priming bolus as well as a period of reduced drug concentration following the priming bolus. This has the potential to lead to adverse events involving drug overdose, under dose, and withdrawal. The adverse events will vary depending on the drug and the drug concentration being infused, but the potential for this to happen is something to be aware of and the patient should be closely monitored after any priming bolus procedure involving intrathecal therapy.

When programming a priming bolus, one should make sure to select the correct drug location and accurately enter the prime volume. The prime volume will vary depending on the location of the drug within the system and the type of procedure (Table 1).

The bridge bolus is used when changing the concentration of the drug or the drug type in the pump reservoir. A bridge bolus is used to clear the previous drug solution from the fluid pathway at the appropriate rate for that concentration (Fig. 9d). Using the bridge bolus in this way can prevent an under dose or an overdose when converting from one drug concentration to another.

Table 1 Type of priming bolus to perform with each different type of pump procedure

Type of procedure	Type of priming bolus used	Notes and tips
Full system implant or pump replacement with aspirated catheter	Prime the internal pump tubing and catheter	To reduce the risk of overdose, consider using a priming bolus of 0.3 mL to fill the internal pump tubing with drug before connecting the catheter and implanting the pump (back table prime). Then program a catheter only after implant
Pump replacement with non-aspirated catheter	Use priming bolus of 0.3 mL to fill the internal pump tubing with drug before connecting the catheter and implanting the pump (back table prime)	Do not prime the catheter
Catheter replacement or catheter contrast study	Prime the catheter only	Internal pump tubing is already primed
Catheter revision: Spinal segment revision	Prime the new spinal catheter segment	Measure the new spinal catheter segment to know what volume is necessary to prime the spinal catheter segment
Catheter revision: Pump segment revision	Prime the new pump catheter segment and the aspirated spinal segment (unrevised spinal segment must be aspirated)	Measure the spinal catheter segments to know what volume is necessary to prime them

The pump reservoir can also be rinsed between changing solutions and concentrations as a significant amount of the previous drug may be present in the pump reservoir even after emptying the pump. Rinsing minimizes the amount of drug present in this residual volume but doesn't eliminate it. The presence of residual drug needs to be taken in account when changing drugs and drug concentrations.

2.2 Ascenda Catheter

There are two types of catheters that attach to the SynchroMed II infusion pump (Fig. 10). Both catheters may be trimmed and are inserted into the intrathecal space by a 16-gauge needle. The catheters are designed for use in the intrathecal space and are initially placed with an internal guide wire. The 8780 model catheter (Fig. 11) is 114 cm and is designed to connect at the pump pocket site and the 8781 model that is 140 cm and is designed to connect near the spinal incision site. The Ascenda™ catheter has a four-layer construction to ensure catheter integrity with high tensile strength and to provide resistance to compression. It is attached to a second catheter that attaches to the pump at its hub (Fig. 11). The ends of the two catheters are joined by a collet (Fig. 11).

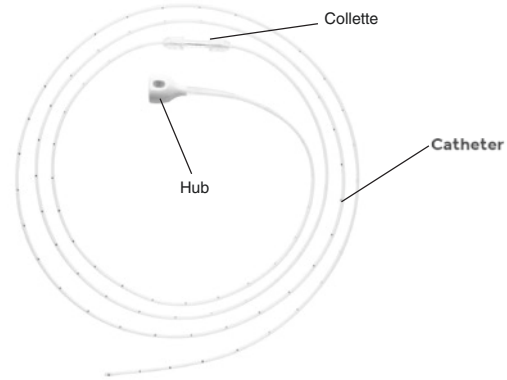

Fig. 11 The Ascenda catheter has two components. The proximal catheter attaches to the pump at its hub and attaches to the distal catheter via a collette

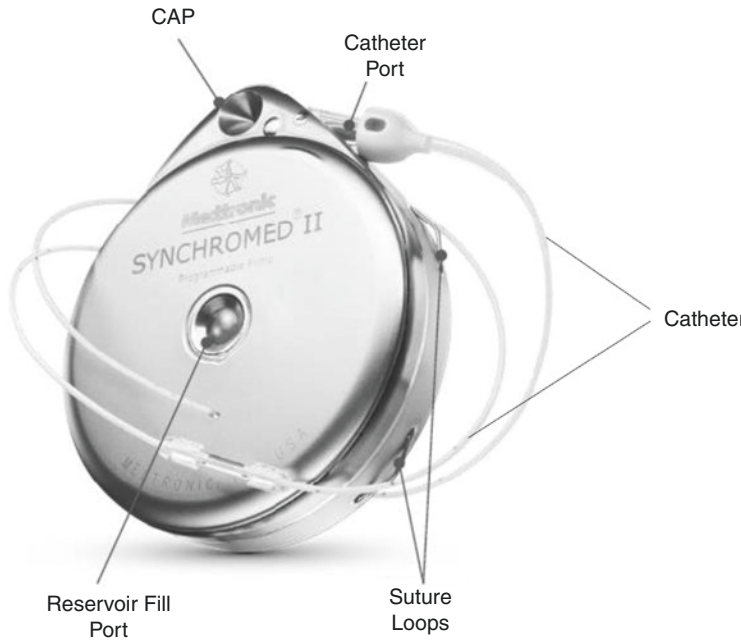

Fig. 10 The SynchroMed II pump with the catheter attached to the catheter port. The two access points to the pump include the reservoir fill port where the medication is added and refilled and the catheter access port (CAP) where the catheter may be aspirated and/or injected. The suture loops are also present on the periphery of the pump and are used to tie the pump down to the underlying fascia during placement of the pump

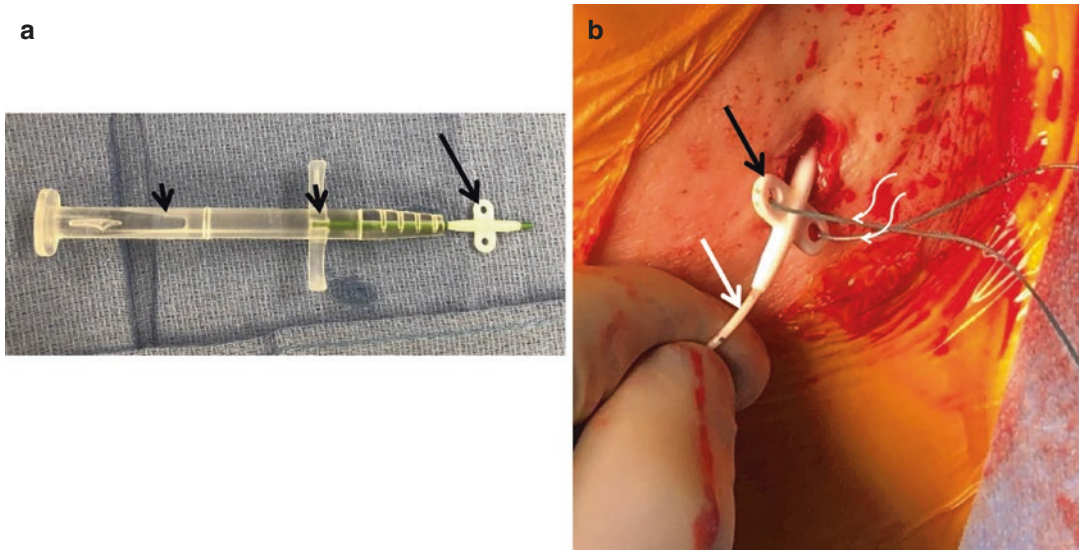

Fig. 12 The catheter is anchored to the fascia by an anchor (black arrows in **a** and **b**) that is placed over the catheter (white arrow in **b**) and deployed using the anchor dispenser (black arrowheads in **a**). The catheter is attached to the underlying fascia with a suture and the ends are passed through the anchor holes (curved white arrows in **b**) and then tied over the suture anchor

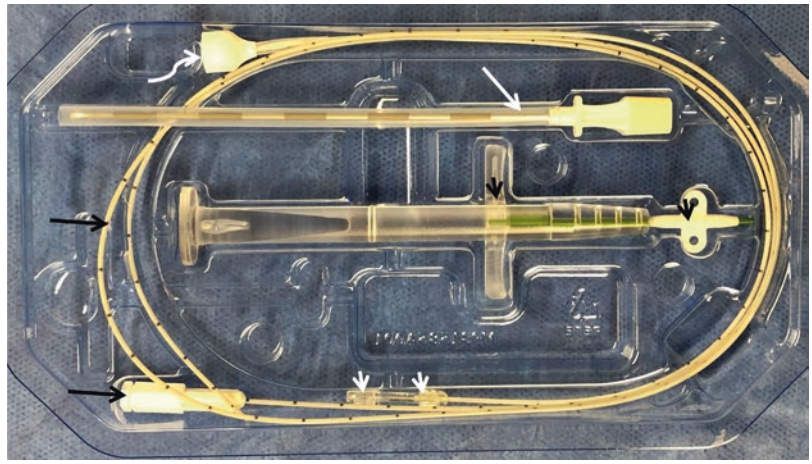

Fig. 13 The catheter insertion kit contains the spinal catheter and an inserted guide wire (black arrows), the Tuohy needle (white arrow), the catheter anchor and anchor dispenser (black arrowheads) and the pump segment of the catheter (curved white arrow) with an attached suture-less connector (the collet) (white arrowheads)

The catheter is attached to the underlying fascia by an anchor placed over the catheter and deployed using the anchor dispenser (Fig. 12a). The most optimal way to anchor the catheter is to loop a permanent suture through the fascia with a single pass oriented axially and to pass the ends of the suture through the anchor holes and tie the suture over the anchor (Fig. 12b). The catheter tip is placed in a location most optimally suited to treat the patient's underlying condition and will vary according to what the treatment goals are.

2.3 Catheter Insertion Kit

The catheter insertion kit comes with the spinal catheter and an inserted guide wire (Fig. 13). The pump segment of the catheter comes with an attached suture-less connector (the collet) (Fig. 13). There is also a 9.1 cm 16-gauge Tuohy needle that comes with the insertion kit that is sufficient for nearly all catheter placements but a longer 15.2 cm 16-gauge Tuohy needle is also available if there is an unusually large amount of

soft tissue to traverse. The catheter anchor comes in the kit preloaded onto the anchor dispenser (Fig. 13). There is also a nonsterile ruler that comes in the kit that is used to measure any portion of the catheter that is trimmed so an accurate catheter length can be determined and programmed into the pump. The product literature is also a component of the catheter insertion kit and can be referred to as an important source of information.

2.4 SynchroMed II Clinician Programmer and Patient Therapy Manager

The SynchroMed™ II pump is a programmable medication infusion device that is controlled via the clinician programmer. The programmer is designed to have simple visual cues that are designed to be intuitive and to facilitate workflow (Fig. 14a). The controller allows the clinician to

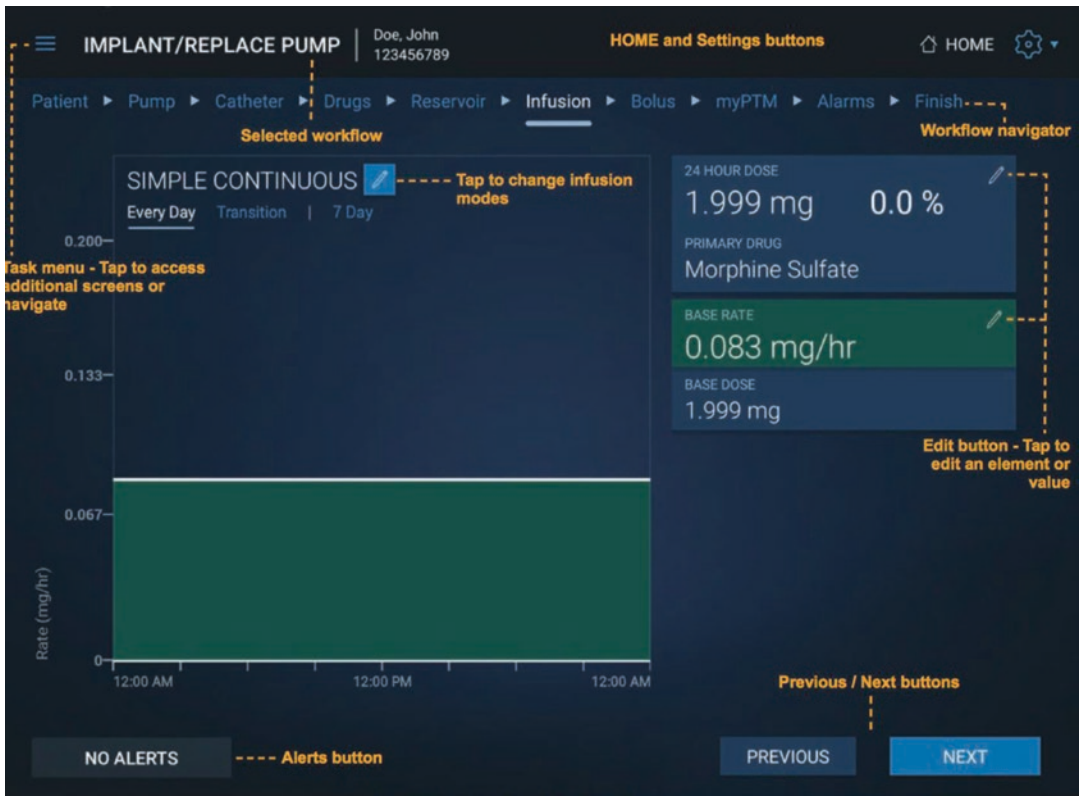

Fig. 14 (**a**) The clinician programmer. The programmer has simple visual cues that are designed to be intuitive. The programmer includes sections on workflow and navigation and has finish screens and action bars (indicated by labels in orange text). After reviewing the pump settings, the user must choose a workflow. The user can navigate through the app by swiping left or right, tapping the task in the workflow navigator, tapping the previous and next buttons or by selecting the tasks using the task menu button. The finish screen is the last screen in every workflow and contains a side-by-side comparison of all program settings. The user must review all settings to confirm pending changes prior to updating the pump. The action bar runs along the top of all screens and contains buttons and indicators. (**b**) The clinician programmer. The clinician programmer is a tablet with a touchscreen interface (**b**) similar to common tablet computers in use currently. (**c**) The communicator. The clinician programmer (right) works with a separate communicator (left) and is designed with wireless connection that enables communication and programming capabilities within a range up to up to 3 m

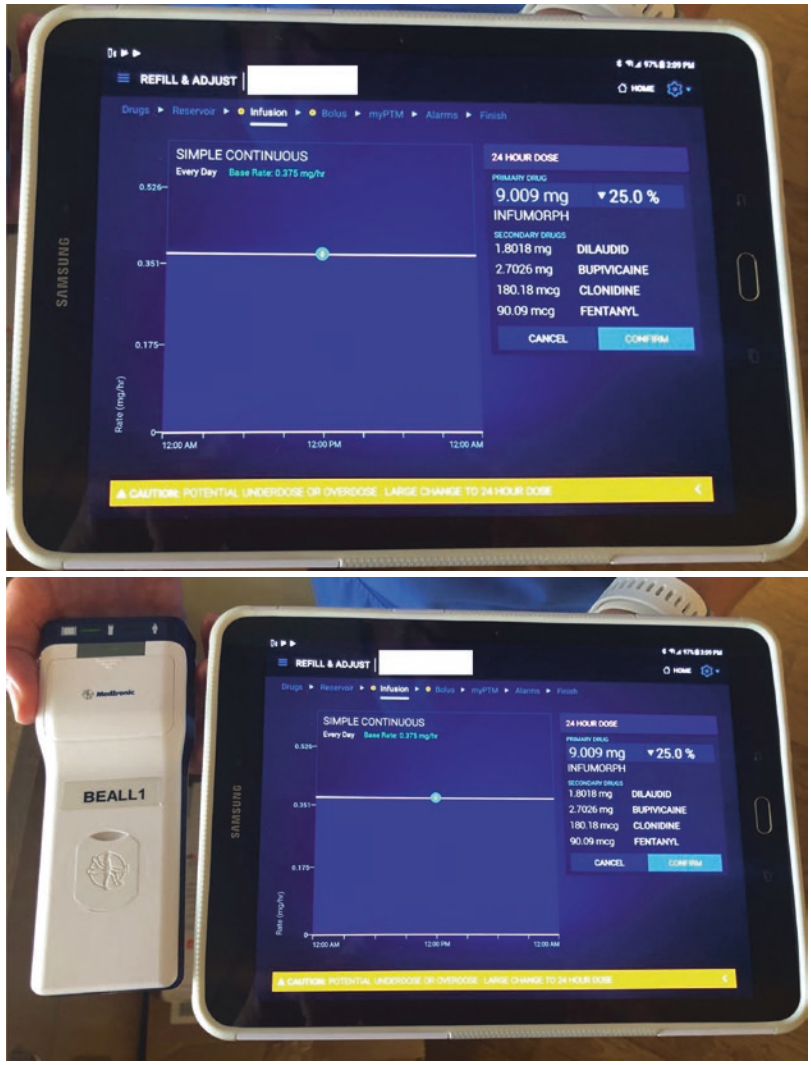

Fig. 14 (continued)

control the daily infusion dose (Fig. 6) and the flex dosing, bolus dosing, priming bolus, and bridge boluses (Figs. 7 and 9) as well as other more complex dosing regimens. The clinician programmer is a tablet with a touchscreen interface (Fig. 14b) similar to common tablet computers in use currently. This tablet interface is compatible with the SynchroMed™ II pump and has workflow guides that facilitate programming, refills, and pump implantation. It has incorporated calculations for fluid volume and rates and has visual indicators that accompany boluses and flex dosing to help facilitate and shorten the process. The clinician programmer works with a separate communicator (Fig. 14c) and is designed with wireless connection that enables communication and programming capabilities within a range up to 3 m.

The communication with the pump is done through standard wireless communication between the communicator that is placed over the pump and the clinician programmer. The programmer accesses the patient data and clinical therapy details that allow for the patient to be followed up at other institutions with the same clinician programming system.

Fig. 15 The Personal Therapy Manager components have a controller that is placed over the pump (black arrow) and the mobile phone device (white arrow) that is the interface with the patient

An additional option for pump management and control may be given to the patient by way of the Personal Therapy Manager (myPTM™) (Fig. 15). This device functions off of a mobile phone and has a simple and patient-friendly design. The clinician can allow for the patient to activate boluses with prescribed and defined medication amounts and bolus dose rates that can serve to help the patients alleviate unpredictable pain without them having to resort to systemic opioids. This on-demand usage provides set amounts to be given a certain number of times during the day separated by predefined amount of time. This patient option allows them to activate a predefined dosage by placing the controller (Fig. 15) over the pump to deliver the bolus dose that is defined by the managing clinician.

In practice, the patient-controlled bolus option has been shown to be associate with higher levels of patient satisfaction with intrathecal pain pump therapy (Ilias et al. 2008). In general, patients report that the screen indicators of bolus confirmations, alerts, and bolus lockouts are very clear and that the myPTM™ is easy to use.

The myPTM™ device is typically used for patients with pain pumps to allow for patient centric treatment of pain but is usually not utilized in patients undergoing ITB therapy.

2.5 Supplies for Intrathecal Pump Implantation

The supplies for implantation of intrathecal pumps will vary according to their availability, the physical location of the pump implantation, physical dimensions of the patient, and physician preference. In general, the following components are essential supplies for implantation of an intrathecal pump: the pump, pump catheter, catheter insertion kit, the clinician programmer, electrocautery, suture to attach the pump, suture for the skin, scalpel, self-retaining retractors, surgical scissors, sterile irrigation, antibiotics, and an abdominal binder. A complete list of supplies necessary for intrathecal pump implantation is listed in Table 2.

Table 2 Sample supply list for intrathecal pump implantation

1. Synchromed II Intrathecal Pump, Ascenda Catheter, SynchroMed II Clinician Programmer, and catheter insertion kit
2. Electrocautery
   (a) The PEAK® Surgery System includes PEAK PlasmaBlade® soft tissue dissection devices and the PULSAR® II Generator.—Medtronic
3. Medtronic Tyrx absorbable antibiotic pouch
   (a) http://www.tyrx.com/index.htm
4. Amniovo Amniotic Membrane Allograft
   (a) 3.0 cm × 3.0 cm size
5. Suture:
   (a) 2-0 Vicryl (2 sutures)
      (i) Deep tissue and subcutaneous skin closure of catheter incision

Suture Construction	Suture Color	Available Sizes	Suture BSR Profile		Absorption complete by:
Braided	Violet/white (undyed)	5/0 through 2	2 weeks	75%	56–70 days
			3 weeks	50%	
			4 weeks	25%	

   (b) 2-0 Ethibond (1 suture)
      (i) Securing catheter anchor

Size:	2-0
Brand:	ETHIBOND
Color:	GREEN
Length:	45 cm/18″
Arms:	Single armed
Material:	Polyester
Construction:	Braided
Absorbability:	Non absorbable
Absorption Rate:	NA
Breaking Strength Retention (BSR):	Indefinite
Directionality:	Unidirectional
Control Release:	N

   (c) 0 Fiberwire Suture (2 sutures)
      (i) Attaching the pump to the abdominal fascia—0 FiberWire, 38″ (blue) w/Tapered Needle, 22.2 mm 1/2 Circle—AR-7250
   (d) Stratafix Suture (1 Suture)
      (i) Subcuticular Closure with 2-0 MONOCRYL® Plus Antibacterial (poliglecaprone 25) Suture
6. Surgical Instruments
   (a) Scalpel and #11 blade
   (b) Self retaining retractors
      (i) Blunt Weitlaner—5.5 to 6.5in
      (ii) Spread Gelpi—5.5 to 7.0 in
   (c) Surgical scissors
7. Sterile saline irrigation
8. Vancomycin powder (3.0 g)
9. Dermabond Prineo wound closure system
   (a) This is a two-part system with an applicator and liquid adhesive 2-octylcyanoacrylate topical skin adhesive (Dermabond) that sets in approximately 60 s when applied to mesh tape
   (b) Patient can shower after Prineo application
10. Abdominal Binder
   (a) Patient wears binder during the day for 2 weeks

3 Intrathecal Implant Technique

3.1 Targeted Drug Delivery Trialing and Preoperative Planning Considerations

Trialing of analgesic medications and intrathecal baclofen has been done for many years and is often performed in patients that are considered optimal candidates for TDD. The patient's response to the trial of intrathecal medication is used to assess if the patient has a sensitivity to the medication and can tolerate the medication and whether the response to the medication was sufficient to warrant pump implantation. Despite the longstanding practice of trialing of intrathecal medications, the most appropriate technique of trialing remains indeterminate based on the expert opinion of clinicians (Deer et al. 2012a).

There are several methods of trialing of medications for TDD, and the medication may be injected into either the intrathecal or epidural space and may be given by using a bolus dose or by continuous dosing. The medication given may be a single medication or a mixture of medications based on the clinician's preference and goals to be accomplished. Because there is limited literature on trialing and a large variation of techniques exists, expert recommendations for trialing as found in the Polyanalgesic Consensus Conference (PACC) are an important addition to the literature and provide a general guide to optimize and standardize one's TDD trialing regimen (Deer et al. 2012a).

3.1.1 ITB Trialing

Since the early use of baclofen, which was approved for intrathecal use in 1984, it has been shown to be safe and effective for the treatment of severe spasticity resistant to oral medications and the medication has been consistently trialed in patients prior to implantation of a TDD delivery device (Penn and Kroin 1984; Hayek et al. 2011a; Patel et al. 2009; Deer et al. 2011). During a trial for ITB, the baclofen is typically injected as a test dose of medication injected into the CSF via a lumbar injection. The injected baclofen is typically very effective in decreasing the patient's spasticity and has been shown to result in decreased muscular tone and a positive response to the screening test in up to 97% of patients with spasticity of spinal origin and up to 86% of patients with spasticity of a cerebral origin (Penn 1992; Gilmartin et al. 2000).

The test is generally conducted as a bolus trial using between 25 and 100 micrograms of IT baclofen in 25 microgram increments injected into the lumbar CSF with a 25-gauge needle using local anesthesia and either conscious sedation or general anesthesia (Rawicki 1999; Awaad et al. 2003). The injection is administered on an outpatient basis by the managing physician at a location that is appropriately equipped for emergency intervention. Prior to the injection the patients are thoroughly evaluated and sometimes videotaped by the physician and physical therapist prior to the injection. There are other key factors that are taken into consideration prior to performing the injection (Table 3). After the injection, the patient is observed in the facility

Table 3 Key considerations for the screening test phase

• Orthotics, seating devices, and other assistive devices should not be assessed or adjusted during a screening test, as response to a bolus is temporary
• Consider holding the morning dose of oral antispasmodic medications prior to screening, abut do not wean altogether, as this changes the patient presentation
• Patients with severe spinal curvatures or fusion may require fluoroscopy to perform a lumbar puncture. This should be determined in advance
• Unrealistic expectations may surface among patients and caregivers during the test; it is important for staff to be prepared to discuss these issues during the screening test
• A family member and/or caregiver should be present for the duration of the screening test to support the patient, receive education, and to occasionally participate in functional assessments
• A lack of documentation may complicate the insurance approval process. Carefully document a lack of response to oral medications and the etiology of a patient's spasticity
• Consider using the same PT/OT and MD to evaluate patients' responses to screening

and assessed for improvement in the Modified Ashworth Scale (MAS), the most commonly utilized rating scale for spasticity (Table 4). Post-injection reassessment of tone is done one or more times between 2 and 4 h after the injection by the physical therapist and around 6 h after the injection by the physician. If videotaping is performed, it is done between 4 and 6 h after the injection? A positive test for either trialing method is defined as a one-point reduction in Ashworth score for spasticity of spinal origin and a two-point reduction in spasticity of cerebral origin. Regardless of the clinician's experience or number of ITB trials that are conducted, a checklist may be used to facilitate optimal consistency of the trials (Table 5)

The single bolus test is generally more effective for lower extremity spasticity than for spasticity in the upper extremities. In patients with spasticity in both the upper and lower

Table 4 Modified Ashworth scale

Ashworth Scale	Degree of muscle tone
0	No increase in tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
2	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement (ROM)
3	More marked increase in muscle tone through most of the ROM, but affect part(s) easily moved
4	Considerable increase in muscle tone passive, movement difficult
5	Affected part(s) rigid in flexion or extension

Table 5 Checklist for intrathecal Baclofen trials

• Perform LP following institution's protocol (in patients with cerebral palsy, measure opening pressure to rule out sub-clinical hydrocephalus)
• Inject appropriate dose of Lioresal Intrathecal given patient diagnosis and other factors (refer to the drug package insert included in this guide)
• Monitor patient vitals every 15 min for an hour, then hourly
• Begin tone assessments around 3–4 h post-injection, using standard scales and institution-specific tools (2–4 h for those with MS)
• Repeat tone assessments every 2 h and document all findings.
• Monitor for complications
• Videotape functional assessments such as:
– Caregivers performing ADLs
– Walking with assistance for patients for whom improved gait is a goal of therapy
– Oral feeding
– Speech
• Document all findings and responses, including peak effect and duration of drug effect
• Instruct patient to lie flat after injection for 1 h (or until assessments are performed) to decrease risk of spinal headache
• Discuss response with patient and family and document their impressions about effect of test dose
• Provide discharge teaching, including clear instructions to resume oral medications
• If initial response to the screening test is less that desired, a second bolus injection may be administered 24 h after the first; reference the drug package insert (included in this guide) for dosing recommendations
After a positive screening test
• Notify implanting physician of test outcome
• Follow up with patient to discuss impressions of the screening test to determine and interest in proceeding with the implant
• Notify medical device company representative of potential implant
• If not done prior to screening test, obtain prior authorization for surgical procedure

extremities, improvement in upper extremity tone and the response to a bolus injection of intrathecal baclofen may be difficult to determine. Additionally, asymmetric spasticity that is much more prominent on one side of the body may create a challenging scenario where a bolus injection may provide optimal relief to the side affected with the spasticity while causing unacceptable weakness on the contralateral side. If the patient assessment after a bolus ITB trial is limited in any of the previously mentioned ways, a catheter trial may be necessary.

As with a bolus trial, the antispasmodic medications are withheld on the morning of the trial and a pre-trial assessment of the patient is conducted by the physical therapist by documenting the MAS scored for each muscle group in the upper and lower extremities (Table 6). Following this, the patient is sterilely prepped and draped and a temporary intrathecal catheter is placed intrathecally from a mid to lower lumbar approach using mild conscious sedation and local anesthesia. The catheter is then advanced to the upper thoracic level (usually between T1 and T4) and then tunneled subcutaneously for 5–7 cm to the lateral flank.

The patient is then taken to an inpatient ward and an intrathecal bolus of 50 μg of bacolofen is given and the patient's MAS is subsequently evaluated at 2 and 4 h post-bolus. A positive test is defined as a reduction of one point on the MAS for spinal or centrally mediated causes of spasticity (Rawicki 1999; Awaad et al. 2003). A secondary, but important end point is the preservation of strength and function in the unaffected extremity.

After the 4-h post-bolus examination, an infusion of a constant dose is begun to find the most optimal dose for a permanent implantation. The initial dose is 100 μg, and this is titrated incrementally in dose changes of 100 μg until an optimal balance is obtained between successfully treating the patients spasticity in the affected extremities and preserving the function in the less affected or unaffected extremities. Once the ideal dose is attained, it is recorded and the catheter removed. The patient is also kept completely supine for 1 h prior to discharge to minimize the chance of a post-dural puncture headache.

While a catheter trial with dose titration may be better than a bolus trial for determing the final affect of the ITB on both the affected and unaf-

Table 6 Modified Ashworth score screening test results worksheet

Spasticity		Pre-bolus (baseline)		2-h post-bolus		4-h post-bolus		6-h post-bolus		8-h post-bolus	
(1–5 to see reverse)		L	R	L	R	L	R	L	R	L	R
Upper extremity	Wrist Flexion:										
	Wrist Extension:										
	Elbow Flexion:										
	Other:										
	Other:										
	Average upper extremity Score:										
Lower extremity	Hip Abduction:										
	Hip Adduction:										
	Hip Extension:										
	Knee Extension:										
	Knee Flexion:										
	Ankle Dorsiflexion:										
	Plantar Flexion:										
	Other:										
	Other:										
	Average Lower Extremity Score:										
Overall Spasm Score (0 to 4—see reverse)											
Overall Pain Score (0 to 10—see reverse)											

fected body parts, the position of the catheter may also be important to optimize therapy for the upper extremities that typically respond less optimally than the lower extremeties. A single shot lumbar dosed bolus may have less optimal affect on the upper extremities than a catheter tip placed at an upper thoracic level (Penn et al. 1989). There is also evidence that placement of the catheter tip at the mid to upper thoracic level may have a positive effect on upper extremity spasticity (Meythaler et al. 1997).

After the patients have been initially identified for ITB therapy and have undergone a successful screening test with a trial of intrathecal baclofen that has produced positive results the patient is considered a candidate for a pump placement that will be discussed below. In addition to the placement of the intrathecal catheter and pump, there will be additional patient visits for rehabilitation and medication dose titration as well as continued medication refills as is necessary.

Prior to placement of the intrathecal pump and even prior to trialing, there should be optimal consideration and discussion of the risks of pump placement and TDD. The safety profile of the SynchroMed II pump has been investigated in a dedicated 1-year study where all investigators reported every adverse event (AE) and categorizing each as either device related or device related (Wesemann et al. 2014). The device-related AEs included those related to the pump, catheter, incisional sites, pump programming, refill procedures, or surgery. Non-device-related events included those related to the intrathecal medication, other medications, and new or worsening of health conditions. In this study, an AE was categorized as serious if it resulted in hospitalization, prolongation of existing hospitalization, a life-threatening situation, persistent or significant disability, permanent impairment, or permanent damage to a body structure, necessity for medical or surgical intervention, patient death, or a congenital anomaly/birth defect.

The authors found that the pumps were accurate and were measured to have delivered within 1–2.5% of the programmed delivery volume, and there were no deaths, permanent injuries, or unanticipated adverse device effects. Adverse events were similar in nature and severity to those described previously (Hayek et al. 2011a; Atli et al. 2010; Flückiger et al. 2008) and in this study the complications requiring surgical intervention were experienced by 14% of subjects, whereas the remainder of system-related AEs resolved following medical intervention. Most of the overall AEs were due to implant site swelling or a spinal headache due to CSF leak and the majority of the device AEs were related to catheter complications such as catheter kinking or catheter rupture. The manufacturer has subsequently introduced a new catheter designed to prevent common catheter complications and posts product performance reports annually at http://professional.medtronic.com/ppr/intrathecal-drug-delivery-systems/index.htm.

The overall risks of ITB and TDD delivery include mechanical failure of the pump, loss of integrity of the intrathecal catheter, and infection around the implanted pump or the catheter. The rate of mechanical failure of the pump and catheter-related issues are not insubstantial and will be discussed in Sect. 5 but one of the most common complications that must be discussed with the patient is a surgical site infection around the implanted pump. The main therapy-related safety issues in patients undergoing IT therapy are related to inadequate patient monitoring for conditions like respiratory depression and issues associated with the medication delivery such as an inflammatory granulomatous mass surrounding the catheter tip. Clinicians must also realize that stopping narcotic medication can cause serious opioid withdrawal symptoms and abrupt cessation of ITB can be life threatening. During the pre-implant conversation with the patient, these risks must be accounted for and taken into consideration before proceeding to intrathecal pump implantation.

3.1.2 Pain Pump Trialing

The risks and process considerations are similar for both ITB and pain pump placement, but the trialing process and goals for the TDD therapy are not. Prior to consideration for pain pump placement the patient typically undergoes a screening test with a trial of pain medication

injected either into the epidural or intrathecal space as discussed above. The expert recommendations for trialing found in the PACC guidelines (Deer et al. 2012a) can provide helpful guidelines for optimizing the process for trialing pain pump patients.

3.1.2.1 Trialing and the Type of Pain

Pain trialing and TDD therapy can be divided into the type of pain to be treated. This includes neuropathic pain, nociceptive pain, and a mixed pain scenario. The algorithms used are different for different types of pain and are generally arranged in a hierarchy based on the literature evidence on safety and efficacy. It should be noted that morphine and ziconotide are the only two agents approved by the FDA for intrathecal use, but the use of other medications is a common practice of pain practitioners who manage IT pumps so it is important to include discussions of these agents and information to facilitate their safe and effective use.

Patients with neuropathic pain are typically trialed with intrathecal preservative-free morphine. This is the only opioid approved by the FDA for intrathecal analgesia. This can be used alone or in combination with the local anesthetic bupivacaine (Line 1 approach in Table 7).

Table 7 Algorithm for intrathecal medications to treat patients with neuropathic pain

Line 1	Morphine	Ziconotide		Morphine + Bupivacaine
Line 2	Hydromorphone	Hydromorphone + Bupivacaine OR Hydromorphone + Clonidine		Morphine + Clonidine
Line 3	Clonidine	Ziconotide + Opioid	Fentanyl	Fentanyl + Bupivacaine OR Fentanyl + Clonidine
Line 4	Opioid + Clonidine + Bupivacaine		Bupivacaine + Clonidine	
Line 5	Baclofen			

Line 1: *Morphine and ziconotide are approved by the US Food and Drug Administration for IT therapy and are recommended as first-line therapy for neuropathic pain. The combination of morphine and bupivacaine is recommended for neuropathic pain on the basis of clinical use and apparent safety*

Line 2: *Hydromorphone, alone or in combination with bupivacaine or clonidine, is recommended. Alternatively, the combination of morphine and clonidine may be use*

Line 3: *Third-line recommendations for neuropathic pain include clonidine, ziconotide plus an opioid, and fentanyl alone or in combination with bupivacaine or clonidine*

Line 4*: The combination of bupivacaine and clonidine (with or without an opioid drug) is recommended*

Line 5*: Baclofen is recommended on the basis of safety, although reports of efficacy are limited*

Adapted from: Deer TR, Prager J, Levy R, Rathmell J, Buchser E, Burton A, Caraway D, Cousins M, De Andrés J, Diwan S, Erdek M, Grigsby E, Huntoon M, Jacobs MS, Kim P, Kumar K, Leong M, Liem L, McDowell GC 2nd, Panchal S, Rauck R, Saulino M, Sitzman BT, Staats P, Stanton-Hicks M, Stearns L, Wallace M, Willis KD, Witt Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation. 2012 Sep-Oct;15(5):436–64; discussion 464–6. doi: https://doi.org/10.1111/j.1525-1403.2012.00476.x. Epub 2012 Jul 2

Table 8 Algorithm for intrathecal medications to treat patients with nociceptive pain

Line 1	Morphine	Hydromorphone	Ziconotide	Fentanyl
Line 2	Morphine + Bupivacaine	Ziconotide + Opioid	Hydromorphone + Bupivacaine	Fentanyl + Bupivacaine
Line 3	Opioid (Morphine, Hydromorphone, or Fentanyl) + Clonidine			Sufentanil
Line 4	Opioid + Clonidine + Bupivacaine		Sufentanil + Bupivacaine OR Clonidine	
Line 5	Sufentanil + Bupivacaine + Clonidine			

Line 1: *Morphine and ziconotide are approved by the US Food and Drug Administration for IT therapy and are recommended as first = line therapy for nociceptive pain. Hydromorphone is recommended on the basis of widespread clinical use ad apparent safety. Fentanyl has been upgraded to first-line use by the consensus conference*

Line 2: *Bupivacaine in combination with morphine, hydromorphone, or fentanyl is recommended. Alternatively, the combination of ziconotide and an opioid drug can be employed*

Line 3*: Recommendations include clonidine plus an opioid (i.e., morphine, hydromorphone, or fentanyl) or sufentanil monotherapy*

Line 4: *The triple combination of an opioid, clonidine, and bupivacaine is recommended. An alternative recommendation is sufentanil in combination with either bupivacaine or clonidine*

Line 5: *The triple combination of sufentanil, bupivacaine, and clonidine is suggested*

Adapted from: Deer TR, Prager J, Levy R, Rathmell J, Buchser E, Burton A, Caraway D, Cousins M, De Andrés J, Diwan S, Erdek M, Grigsby E, Huntoon M, Jacobs MS, Kim P, Kumar K, Leong M, Liem L, McDowell GC 2nd, Panchal S, Rauck R, Saulino M, Sitzman BT, Staats P, Stanton-Hicks M, Stearns L, Wallace M, Willis KD, Witt Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation. 2012 Sep-Oct;15(5):436–64; discussion 464–6. doi: https://doi.org/10.1111/j.1525-1403.2012.00476.x. Epub 2012 Jul 2

Consistent with the recommendations of the 2007 Polyanalgesic Consensus Conference guidelines, ziconotide may be used as a first-line medication for both neuropathic and nociceptive pain (Deer et al. 2007).

The second-line approach (Line 2 approach in Table 7) involves hydromorphone either as single drug therapy or in combination with bupivacaine or clonidine. Morphine may also be used in combination with clonidine as a second-line option for patients with neuropathic pain.

The third-line approach (Line 3 approach in Table 7) consists of using fentanyl either alone or combined with bupivacaine or clonidine. Monotherapy with clonidine is also a consideration for third-line therapy as is a combination of ziconotide and morphine or hydromorphone.

The fourth-line approach (Line 4 approach in Table 7) involves a combination of bupivacaine and clonidine, with or without an opioid and a fifth-line approach to patients with neuropathic pain is monotherapy with ITB (Deer et al. 2012a).

Patients with nociceptive pain are treated with a somewhat different treatment algorithm. A first-line approach (Line 1 approach in Table 8) used morphine, hydromorphone, ziconotide, and fentanyl. Fentanyl may be used as a first-line medication given its good long-term use history and low incidence of granuloma formation (Allen et al. 2006; Fukushima et al. 2011) and the lipophilic characteristic of fentanyl optimizes its efficacy in treating pain.

The second-line approach (Line 2 approach in Table 8) for nociceptive pain is done with bupiva-

caine combined with morphine, hydromorphone, or fentanyl. A combination of ziconotide and an opioid medication may also be utilized as a second-line treatment approach.

The third-line approach (Line 3 approach in Table 8) consists of either sufentanil monotherapy or a combination of an opioid (i.e., morphine, hydromorphone, or fentanyl) and clonidine (Deer et al. 2012a).

The quaternary approach (Line 4 approach in Table 8) for nociceptive pain includes combining an opioid with clonidine and bupivacaine or combining sufentanil with either bupivacaine or clonidine.

The fifth- and last-line approach (Line 5 approach in Table 8) consists of a triple combination of sufentanil, bupivacaine, and clonidine. This combination should be reserved for the patients with the most refractory type of pain.

There will be, of course, patients with pain that has mixed characteristics of neuropathic and nociceptive pain and scenarios where the exact type of pain is difficult to identify. In these cases, the primary clinical characteristics should guide the decision-making process as to which medication or medication combination to choose. This may also include a wholesale change in medication choice or combination therapy choice after the patient is re-evaluated.

3.1.2.2 Trial Dosing and Method

After the appropriate medications have been chosen, the treating physician should consider what dosage of medication should be started after the implantation of the intrathecal pump. These starting dosage ranges of IT medications have been recommended by the Polyanalgesic Consensus Conference guidelines and are listed in Table 9. These starting dosages may vary, especially with opioids and the patient's tolerance based on their baseline intake amount and on the chronicity of the medication ingested.

The trialing process itself may be done for patients prior to and in preparation for pump implantation or in patients with existing implanted pumps when a change in intrathecal medication is being considered. The trialing process is based on the postulation that it will provide information on the effectiveness of the medication and will test to make sure the patient doesn't have an adverse reaction to the medication injected. Some of the issues related to chronic therapy such as the increasing tolerance to opioid medication and the subsequent opioid-induced hyperalgesia (OIH) can't be evaluated in the short term during the trial and the trialing process may underestimate the long-term failure rate of TDD.

Another issue to be taken into consideration when considering a trial of intrathecal medication is the disease process involved and the life expectancy of the patient. Many experts believe that trialing is not needed in patients with cancer of a limited life expectancy and that if they have tolerated the medication when given via another route then intrathecal trialing is not necessary.

As mentioned previously trialing can be performed by injecting medication either intrathecally or into the epidural space. Many practitioners hold the opinion that epidural trials are not optimally helpful in determining the response to the medication given the fact that the epidural space has a different extent, surface area, and absorptive characteristics than does the intrathecal space. Despite this anatomic targeting difference

Table 9 Recommended starting dosage ranges of intrathecal medications

Drug	Recommended starting dosage
Morphine	0.1–0.5 mg/day
Hydromorphone	0.02–0.5 mg/day
Ziconotide	0.5–2.4 mcg/day
Fentanyl	25–75 mcg/day
Bupivacaine	1–4 mg/day
Clonidine	40–100 mcg/day
Sufentanil	10–20 mcg/day

Adapted from: Deer TR, Prager J, Levy R, Rathmell J, Buchser E, Burton A, Caraway D, Cousins M, De Andrés J, Diwan S, Erdek M, Grigsby E, Huntoon M, Jacobs MS, Kim P, Kumar K, Leong M, Liem L, McDowell GC 2nd, Panchal S, Rauck R, Saulino M, Sitzman BT, Staats P, Stanton-Hicks M, Stearns L, Wallace M, Willis KD, Witt Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation. 2012 Sep-Oct;15(5):436–64; discussion 464–6. doi: https://doi.org/10.1111/j.1525-1403.2012.00476.x. Epub 2012 Jul 2

and the difference in absorption of the medication, there is a pronounced literature deficiency in investigating this issue and there are no prospective studies showing an advantage for predictability of success for intrathecal or epidural trialing.

Much of the use of TDD is in patients who have been on high doses of oral pain medications chronically. The longer the patient is on opioid medication and the higher the dose, the greater the risk of OIH. This scenario can complicate the trialing process by introducing an opioid tolerant patient who is very sensitive to pain.

The prevailing opinion regarding OIH is that an opioid-naïve brain would be ideal for trialing and more predictable than patients who are very tolerant to opioid medications. Lower doses of IT medications can be used in opioid-naïve patients and, because of the better safety profile, is preferable to using much higher dosages. The appropriate opioid dose conversions to derive an appropriate dose for IT opioid trialing when considering the patients' oral and/or transdermal dosing is debatable because of differences in tolerance to the medications, differences in the length of time the patient has been on the medication and the pre-trial weaning schedule of the patients systemic opioids. In some situations, the patient's pain producing process and pain severity will not allow for reducing the opioid dose prior to trial.

As discussed above, in patients who have neuropathic pain trialing with ziconotide should be considered. Trialing with this medication can be difficult because side effects of the drug are more prominently related to the rate of dosage increase than to the absolute dosage. Because of this trialing with bolus dosing can be helpful to select some appropriate candidates but the side effects related to bolus dosing may eliminate many patients who might otherwise be very good candidates IT ziconotide therapy. Catheter trialing may be impractical and difficult because of the slow titration required with ziconotide. The trialing doses range from one to five micrograms per bolus (Table 10), but catheter dose increases range from 0.5 to 1.0 mcg every several days. Using the appropriate trialing method to avoid a trial failure due to intolerable side effects is essential to identify the appropriate patients for ziconotide treatment.

Table 10 Recommended dosage of medications for intrathecal trialing

Drug	Recommended IT bolus dose
Morphine	0.2–1.0 mg
Hydromorphone	0.04–0.2 mg
Ziconotide	1–5 mcg
Fentanyl	25–75 mcg
Bupivacaine	0.5–2.5 mg
Clonidine	5–20 mcg
Sufentanil	5–20 mcg

Adapted from: Deer TR, Prager J, Levy R, Rathmell J, Buchser E, Burton A, Caraway D, Cousins M, De Andrés J, Diwan S, Erdek M, Grigsby E, Huntoon M, Jacobs MS, Kim P, Kumar K, Leong M, Liem L, McDowell GC 2nd, Panchal S, Rauck R, Saulino M, Sitzman BT, Staats P, Stanton-Hicks M, Stearns L, Wallace M, Willis KD, Witt Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation. 2012 Sep-Oct;15(5):436–64; discussion 464–6. doi: https://doi.org/10.1111/j.1525-1403.2012.00476.x. Epub 2012 Jul 2

The recommended doses for IT trialing are shown in Table 10. These doses are most often determined by the patients' preoperative medications. Fluoroscopic guidance should be used to guide the IT bolus injection best delivered with a 25-gauge needle and the dosing should be followed by a period of extended patient observation, preferably overnight. The use of constant infusion also required extended following and careful titration and hospital admission unless this technique is used as a palliative approach at the end of life.

Just as with ITB, the trialing method may be by either using a bolus dose or by using an IT catheter. As mentioned previously the trialing may be performed by injecting medication either intrathecally or into the epidural space. There are advantages and disadvantages to each of the trialing methods and disagreement exists regarding many aspects of the trialing process. For example, there is no consensus on the degree of pain and symptom relief that should be used to assess the effectiveness of a trial, and there have been no studies done to assess why certain patients have a failed trial.

There is also no consensus and no studies done on the most appropriate technique for trialing. Trials have been performed with bolus doses into the IT or epidural space but longer term (days to weeks) trialing with catheters placed into these two spaces have also been done with repeated or constant dosing of medication. The position of the catheter tip used during the trial may also be important in addressing the patient's pain, but there has been no studies evaluating this either.

Most practitioners use their experience and rationale to guide their trialing, and this typically involves performing a trial that best mimics the type of therapy and system that would be used if the patient were to be implanted with a permanent system. As with any type of chronic opioid use, there will be some medication tolerance that will develop and the initial bolus dose that was shown to be effective initially may not continue to be effective over time. That being said the rate of dose escalation is not nearly the same as is seen with oral opioid medications and the overall dose is far lower with IT therapy, and there is some evidence that suggests that long-term responsiveness is correlated with the initial dose that is needed to achieve pain control (Dominguez et al. 2002).

3.1.2.3 Whether or Not to Trial

Although there is no literature base upon which to either support or discourage pre-implantation trials, the preliminary trialing is generally recommended. The trialing technique and the criteria for the definition of a positive trial vary substantially and primarily depend on the clinical context of the patient being treated. The British Pain Society has published recommendations for the best clinical practice for intrathecal drug delivery for pain and spasticity (British Pain Society 2008) and their panel supported conducting trials prior to the implantation of every targeted drug delivery system. The panel also supported using either a single bolus or continuous infusion according to the patient's specific clinical scenario. Finally, they recommended that each practitioner develop a trialing protocol for their own practice that is based on safety, adherence to known algorithmic principles, and adequate patient monitoring (British Pain Society 2008).

Before considering a trial, it should be known that there are patients for whom trial may not be necessary. These most commonly include patients with pain related to cancer, but other factors may be taken into consideration as well such as the patient's life expectancy, the nature of the underlying disease, and whether there are socioeconomic factors that may preclude a trial. Additional details regarding patients for whom trialing may be unnecessary are provided in the brief report Polyanalgesic Consensus Conference-2012: Consensus on Trialing for Intrathecal Drug Delivery (Deer et al. 2012a).

3.1.2.4 Dosing and Medication Selection

The trial dosing and medication choice are essential components to understand prior to conducting a trial. Morphine has remained the standard first-line therapy because of its long duration of action and ease of use (Krames 1993). Other opioid medications such as meperidine, hydromorphone, fentanyl, sufentanil, and methadone have all been used in the epidural and intrathecal space (Krames 1993; Foley 1985). The pharmacokinetics and distribution of the medication are all related by the opioid's lipid solubility and opioid receptor affinity (Table 11). The time of onset, duration of action, the availability of the medication to the CNS, and the uptake and distribution are all related to these two factors. Morphine has a relatively high opioid receptor affinity and low lipid solubility and therefore enters the lipid substance of the spinal cord slowly but remains bound to the opioid receptors for a long time period. The onset of action may take 1–3 h but

Table 11 Receptor affinity and solubility of opioid drugs

		Solubility	
Drug	Affinity	Lipid	Water
Morphine	High	Low	High
Dilaudid	High	Low	High
Fentanyl	Low	High	Low
Sufentanil	High	High	Low

Adapted from: Krames ES. Intrathecal Infusional Therapies for Intractable Pain: Patient Management Guidelines. J Pain Symptom Manage 1993;8:36–46

the duration is typically between 12 and 24 h and because of its low lipid solubility it tends to stay in the CSF where it ascends to the supraspinal anatomy via the normal CSF flow. The supraspinal flow may also contribute to side effects including sedation, respiratory suppression, and nausea and vomiting.

The dosing of the opioid use for trialing (also used as the starting dose for treatment after implant placement) is calculated empirically from the patient's daily opioid use also taking into consideration the duration of oral or transdermal opioid treatment. The initial dose estimate can be determined by using the calculation that has proven clinically useful. First, convert the patient's 24-h oral morphine requirement to a 24-h intramuscular requirement (Table 12). If the patient is taking other opioids convert those to the intramuscular morphine equivalents (Table 12) but give only one half of that dose due to incomplete opioid cross tolerance. The epidural dose is equal to the 24-h intramuscular equivalent morphine dose divided by ten, and the IT dose is equal to the epidural dose divided by ten. This results in an IT dose that is approximately a 1:300 ratio to the oral dose. This dosing is effective for patients on low dose opioids or for patient who are narcotic naïve but for patients who are on higher doses of opioids the ratio may be 1:100 or higher.

Patients also may require weaning of their systemic opioids prior to the trial and the permanent implant placement. Previous weaning methods describe an initial decrease of 50% of the total daily morphine equivalent dose prior to the trial followed by an additional 50% prior to the permanent pump implantation (Hamza et al. 2012). An alternate method is to wean the patients 50% prior to the trial followed by additional 20% dose decreases per day. During any of the dose decreases, the patient must be observed closely for withdrawal symptoms and placement of a clonidine patch or the use of lofexidine may be necessary if the withdrawal symptoms are sufficiently severe.

Table 12 Equianalgesic dosing

Narcotic agent	Route	Equianalgesic dose (mg)
Morphine	IM	10
	PO	30
Hydromorphone	IM	1.5
	PO	7.5
Meperidine	IM	75
	PO	300
Methadone	IM	10
	PO	20

IM intramuscular; and PO, oral. The IM-PO morphine ratio of 1:3 is conventionally used during chronic dosing
Adapted from: Foley KM. Treatment of cancer pain. N Engl J Med 1985;313:84–95

3.1.2.5 Side Effects

In most institutions, a 50% reduction in pain is stated to be a positive trial and patients are also observed for side effects such as mentioned above with the most important side effect being respiratory depression. Also though this is rarely seen in opioid tolerant patients, the incidence of respiratory depression with intrathecal injections in opioid-naïve patients can be as frequent as one in 275 patients (Rawal et al. 1987). Nausea and vomiting are common side effects in opioid-naïve patients and are most common with the hydrophilic medications as compared to the more lipid soluble agents such as sufentanil, meperidine, and fentanyl.

All opioids inhibit the micturition reflex and spinal administered opioids appear to inhibit this more than systemic opioids. This inhibition and resulting urinary retention is typically worse in males than in females and can be reversed by low dose naloxone (Hustad et al. 1985).

Pruritus is also a very common side effect that is typically dose dependent and is more common in patients with nociceptive and neuropathic pain than in patients with cancer-related pain. This symptom, like urinary retention, is self-limited and typically can be controlled with diphenhydramine and/or low dose naloxone.

3.1.2.6 Trial Environment

After injecting pain medication into the intrathecal space, most practitioners agree that the patient needs to be monitored for at least 24 h. Preferably,

this monitoring would be in an inpatient or similar environment and is especially important for bolus trials and trials using short-acting intrathecal opioids. Patients that are stable a day after an IT injection of opioids or that have normal neurologic function 12 h following a bolus trial of ziconotide may be discharged.

Prior to discharge and throughout the trial is necessary to track the patients response to the IT medication in regard to their vital signs, overall level of pain and level of pain while performing such activities as sitting, standing, walking, or lying down (Table 13). The dose of the medication should be recorded along with the time it was given and whether or not the patient's daily medications were held or dosage altered. It is also helpful to record the location of pain, the goals of the trial, and what the outcome of the trial was in regard to the amount of pain reduction and whether the trial was successful or not (Table 13).

3.1.2.7 Comorbidities and Medication Interaction

Prior to trialing comorbidities should be determined and a full medication list with dosing regimens should be obtained. Certain comorbidities are important to note including sleep apnea, a compromised immune system, diabetes, and urinary tract obstruction as intrathecal medications can potentially exacerbate these underlying conditions or interact with them to cause additional issues (Walker et al. 2007). For example, patients with underlying immunocompromised states may require antibiotics that are not normally given for an intrathecal medication trial (Mangram et al. 1999). Similar to other types of injections, anticoagulant medications should be stopped before undergoing an intrathecal injection (Horlocker et al. 2010). Medication interactions that produce adverse effects should be known and assessed for including benzodiazepines. Benzodiazepines and opioids

Table 13 Screening test results

Patient Name:			Date:				
Dose Given:		Time of Injection:		Oral Medications: o Withheld o No change o Other:_____			
Dose Location:	Pre-trial	Hours after initial dose	Hours after initial dose	Hours after initial dose	Hours after initial dose	Hours after initial dose	Hours after initial dose
Check Vitals	HR	HR	HR	HR	HR	HR	HR
	BP	BP	BP	BP	BP	BP	BP
	O2	O2	O2	O2	O2	O2	O2
Pain Scale:	**1–10**	**1–10**	**1–10**	**1–10**	**1–10**	**1–10**	**1–10**
Sitting:							
Standing:							
Walking:							
Lying:							
Other:							
Other:							
Other:							
Pain Location:							
Primary Goals Achieved With Screening Test:							
Recommendations: • Successful screening test; schedule surgical consult • Unsuccessful screening test; schedule to repeat test at higher dose • Unsuccessful screening test; patient not a candidate for pain pump							
Comments (clinician observations, patient comments)							

have synergistic effects and can have adverse effects on the patients breathing and the ability to maintain adequate oxygenation. In general, benzodiazepine medications are not used in patients with intrathecal pumps due to the increased risk of respiratory depression, and these medications should be not be taken prior to a intrathecal injection of opioids (Coffey et al. 2009). In rare cases where the benzodiazepine medication cannot be eliminated or reduced in dose the amount of opioid administered should be decreased. Doses of other medications should be kept unchanged for the trial so that the intrathecal medication is the only variable.

Prior to the intrathecal injection of medication the patients existing pain medications can be handled in one of three different ways. The dose of opioids can remain the same with no modification prior to the trial or the opioid dose can be reduced with a typical target of half of the current dose. Alternatively, the patient can be weaned off all systemic opioid medications prior to the trial. In general, the lower the dose of systemic opioids, the better the patient's response will be to an appropriately dosed intrathecal opioid medication. If the patient is taken off opioid medications at least 6 weeks before the trial, it may reduce the impact of opioid-induced hyperalgesia (OIH) which can certainly be beneficial for the patient in regard to sustained analgesia following the intrathecal injection and in determining whether the OIH was responsible for a portion of the patient's continued pain (Angst and Clark 2006b). The process of weaning down a patient's systemic opioids may also result in the reduction or elimination of the patients OIH and if they are sufficiently better placement of the pump may not even be necessary.

3.1.2.8 Complications of Trialing

Complications associated with an IT injection of opioid medication are unusual but certainly can occur. One of the most severe complications that can occur is meningitis that results from the IT injection. This is treated by prompt administration of appropriate intravenous antibiotics and supportive care as is necessary. Headaches after dural puncture can happen at a frequent rate with larger gauge needles but is very uncommon after an IT injection with a 25-gauge needle (Ahmed et al. 2006). The reported rate of spinal headache after dural puncture is stated to be as high as 12% after penetration of the dura with a 24- to 27-gauge needle, but other authors have found a rate of 6% for 24-gauge needles (Vandam and Dripps 1956). In this chapter, authors' experience the rate of post-dural puncture with a 25-gauge spinal needle following an intrathecal trial is less than 1%. Post-dural puncture headaches can be managed by performing an epidural blood patch which is typically very effective at relieving the patient's symptoms, but less invasive methods can also be used including fluid loading, caffeine ingestion, or the medication theophylline. Another potential complication of IT trialing is urinary retention. In cases of prominent urinary retention, the patient may have to undergo catheterization or placement of a temporary Foley catheter. Hypotension after IT opioid has been described and is typically treated with adequate intravenous fluids and proper monitoring of the patient's vital signs (Minville et al. 2006).

3.1.2.9 Catheter Dislodgement

Although catheter dislodgement during trialing is unusual, it is important to understand how to adequately secure the catheter in order to prevent or limit this post-procedure complication. The entry point of the catheter should be placed in the mid to lower lumbar spine as this is a less mobile part of the spine compared to the thoracolumbar junction and lies below the conus medullaris portion of the spinal cord. The additional length of catheter placed in the intrathecal location will help to keep the catheter located in an intrathecal position. The catheter should also be anchored adequately by using an adhesive device or other anchoring mechanism that securely holds the catheter. The catheter can also be tunneled the length of a 3.5-inch needle and secured with a suture. If dislodgement of the catheter does occur, the catheter can either be replaced or the trial can be terminated and repeated at another time.

3.1.2.10 Psychological Fitness for Trialing

A patient's psychological status and willingness to participate in an intrathecal trial should be evaluated. The patient's expectations must be accurate, and this should be discussed extensively prior to conducting the medication trial. The patient should also be psychologically stable prior to proceeding with the trial and ideally should have an adequate and supportive social support network (Deer et al. 2010b).

3.2 Appropriate Patient Positioning

Prior to patient positioning they are anesthetized. Clinical experience indicates that an awake but sedated patient may be the best scenario for the individual undergoing the procedure to complain of pain or paresthesia as an indicator of an adverse neurological event, but the degree of invasiveness of an intrathecal pump placement and the length of time necessary to place the pump and catheter may make it preferable to have the patient anesthetized with either spinal or general anesthesia (Deer et al. 2012b). It has been recommended by the Polyanalgesic Concensus Conferences that the choice of anesthetic should be left to the managing clinician and tailored to the patient's best interest (Deer et al. 2012b).

After the appropriate anesthesia is applied, the patient is put into position. The pump is typically placed just over the anterior abdominal wall in either the right or the left lower quadrant. In patients with little subcutaneous fat, pumps can be placed in a subfascial plane (Ammar et al. 2012) and other sites of placement have been identified when necessary including the subclavicular location, the anterior thigh, and the mid portion of the abdomen (Devine et al. 2016). In cases with anatomic impediments to the typical placement or for patients with increased skin tension on the overlying abdomen or in patients with severe morbid obesity an alternative pump placement site may be necessary.

Prior to implantation, it should be discussed with the patient which location and which side to place the pump. It should be noted that the only on-label location for the pump is adjacent to the abdomen in either the right or left lower quadrants. The pump is placed along the midclavicular line equidistance between the inferior costal margin and the iliac crest.

Antibiotic prophylaxis is given at least 30 min prior to placement of the incision. Following this, the patient is anesthetized and positioned in the lateral decubitus position on the operating room table with the side of the pump placement upward and the patient placed on a surgical beanbag immobilizer or something similar to hold their position (Fig. 16). The patient is then sterile prepped and draped and a C-arm is put into place to guide access to an intrathecal location and for the positioning of the catheter tip (Fig. 16).

3.3 Key Steps in Pump Implant Procedure

The steps in placing a functional intrathecal pump apparatus include placement of the catheter, preparation of the pump pocket, catheter tunneling, catheter and pump connection, and the placement of the pump along the anterior abdominal wall in the right or left lower quadrant of the abdomen. A complete list of supplies necessary for the placement of an intrathecal pump can be found in Table 2.

3.4 Catheter Placement

Following appropriate patient and C-arm positioning, the placement of the catheter is the first portion of the procedure. The C-arm is moved into place and the needle is placed into the intrathecal location with fluoroscopic guidance and a paramedical approach usually at the L2-3 to L4-5 levels depending on the patient's underlying anatomy but whenever possible the catheter entry point should be below the conus medullaris to avoid spinal cord injury. A slight to moderate cephalad angle is placed on the needle to decrease the risk of catheter kinking at the intrathecal

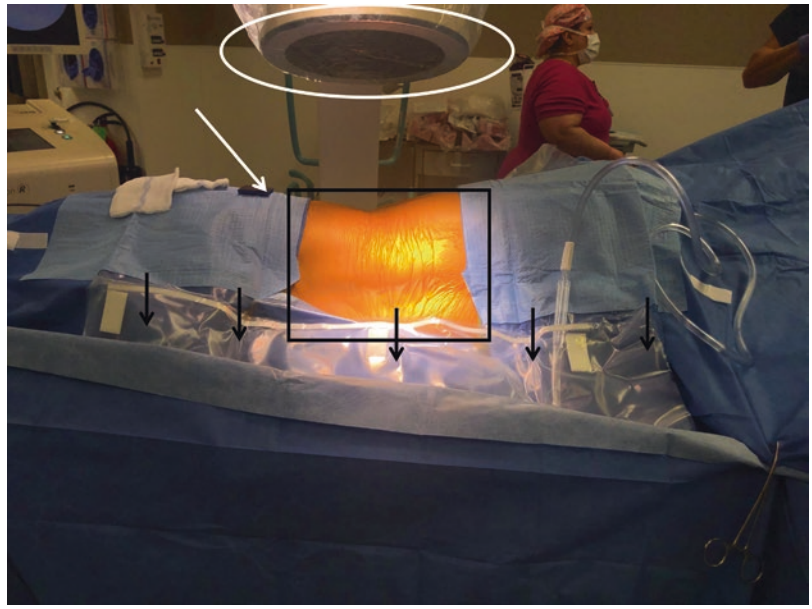

Fig. 16 Patient positioning on the operating room table in a right lateral decubitus position with the left side up (white arrow) and the surgical site prepped (area within the black rectangle). The surgical beanbag immobilizer is placed beneath the patient (black arrows) but the visualization of the beanbag itself is blocked by the overlying blue surgical drapes. The C-arm is seen to be in place over the patient (white oval)

entry point and to make the threading of the catheter easier.

After appropriate needle placement, the CSF should be evident flowing back through the needle and then catheter is subsequently placed into the intrathecal space and advanced to the target position under intermittent fluoroscopic guidance (Fig. 17). The catheter tip placement should be determined after a complete evaluation of the patient's anatomy and the primary anatomic target of the therapy (Jose de et al. 2013).

After placement of the catheter, a 1–3 cm incision is made around the catheter entry site with a scalpel and the needle in place or with electrocautery after removing the needle (Fig. 18a). The catheter anchor is then inserted over the catheter and anchored to the underlying lumbodorsal fascia with a permanent non-resorbable suture (Fig. 18b). During the placement of the anchor suture, the Tuohy needle should either be kept in place or the catheter moved cranially to protect it from being injured by the suture needle. The wire is then removed from the catheter and the presence of CSF flow is again confirmed. Following this confirmation, a hemostat or other clamp is placed on the proximal end of the catheter to prevent loss of CSF. The incision is then covered with a sterile gauze sponge and attention is turned to the lower quadrant of the abdomen where the pump is to be placed

3.5 Pump Pocket Preparation

In the lower quadrant of the abdomen in the midclavicular line, halfway between the iliac crest and the lower costal margin a 7-cm incision is made through the skin and superoinferior traction is applied as the incision is continued through the subcutaneous fat typically using monopolar electrocautery (Fig. 19a). The incision is extended down to the fascia of Scarpa, which is the deep membranous layer of the fascia of the abdomen, which lies just superficial to the external oblique muscle. This fascia is thin and membranous and pulls off the rectus sheath and the external oblique muscle with retraction of the subcutaneous fat. This provides a natural plane that, when dissected out, provides a pocket for the pump to sit on top of the external oblique muscle sheath. The pocket created in this location should just be large enough for the pump and capacious enough to allow closure of the soft tissue over the pump without tension. The depth of the pocket is also important as a depth greater than 2.5 cm may not allow for reliable communication with the pump

Fig. 17 Lateral fluoroscopic view of the upper thoracic spine shows an intrathecal catheter and its radiopaque catheter tip (white arrow) just posterior to the T2-3 intervertebral disc

controller and can make refilling the pump more difficult.

Hemostasis is important to maintain at both incision sites, especially in the lower quadrant abdominal incision, as this wound tends to have more blood vessels. The hemostasis is typically easily attained using simple electrocautery. After the pocket has been created and the bleeding from the incision has been controlled four permanent sutures are placed at the anchor points of the pump. The sutures are placed though the tenacious covering of the external oblique muscle taking care to make a horizontally oriented pass through this portion of the abdomen to not injure the bowel that can be closely underlying the anterior abdominal wall (Fig. 19b). The sutures should be placed prior to placing the pump in the pocket to make the pump insertion and suture anchoring easier.

3.6 Catheter Tunneling

Next the malleable tunneling device is used to create a subcutaneous tunnel from either the paramedian lumbar incision to the abdominal pump pocket or vice versa (Fig. 20). It is often easier to tunnel from the abdominal pocket to the smaller lumbar incision, but this should be assessed on a case-by-case basis based on the patient's anatomy and the potential difficulties encountered during the tunneling process. Once the tunneling has been accomplished the catheter is placed through the lumen of the tunneling device and it is removed. The excess catheter is trimmed leaving about 5–10 cm of catheter present in the location of the pump pocket. The trimmed portion of the catheter is measured, and this should be recorded so the final catheter length will be accurate. The amount of catheter present in the abdominal pocket will be lengthened by the proximal catheter attachment (Fig. 21), and the amount of total catheter length should be enough for a stress relief loop to be formed in the catheter pocket to ensure enough slack so as not to cause retraction of the intrathecal portion of the catheter with patient movement. The catheter should also not be left too long as this could increase the susceptibility to catheter kinking.

3.7 Catheter and Pump Connection

After tunneling the catheter is attached to the pump and the excess catheter is placed in loose coils behind the pump and the pump is placed inside the pocket and attached to the anterior abdominal with permanent sutures placed through the loops on the side of the pump. Prior to placing the pump in the pocket the catheter attachment hub is checked to make sure it is

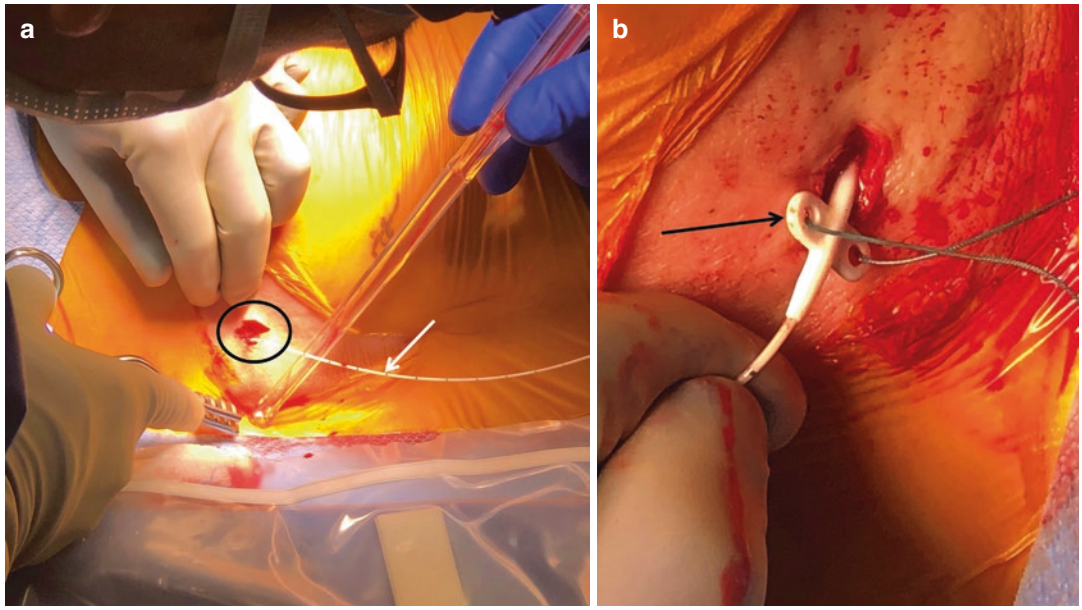

Fig. 18 (**a**, **b**) An incision (black circle in **a**) is made around the catheter (white arrow in **a**) and then the catheter anchor (black arrow in **b**) is inserted and anchored to the lumbodorsal fascia

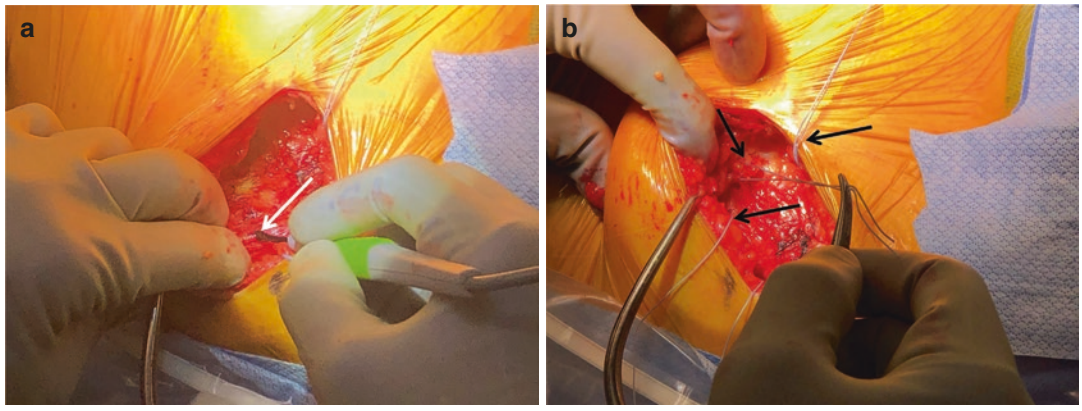

Fig. 19 (**a**, **b**) The lower quadrant abdominal incision is made through the skin and down through the subcutaneous fat usually using electrocautery (white arrow in **a**). Permanent sutures are placed through the anterior portion of the abdominal wall (black arrows in **b**), which will later be used to secure the pump to the anterior abdominal wall

securely attached to the pump and rotates freely at the attachment site.

Subsequent to placement of the pump, the pocket and catheter entry site is irrigated with a sterile saline and Betadine and/or antibiotic solution. Additional antimicrobial measures can also be taken including adding an absorbable antibiotic pouch such as the Tyrx™ antibacterial envelope and/or by adding a powdered antibiotic such as Vancomycin. The Tyrx™ pouch was originally designed for implantable cardiac devices and is made from an absorbable surgical mesh comprised of two antibiotics (minocycline and rifampin) (Kolek et al. 2013). It was originally designed to help stabilize the device and to reduce the risk of infection. While the infection reduction has been demonstrated in implantable cardiac devices (Kolek et al. 2013; Krahn et al.

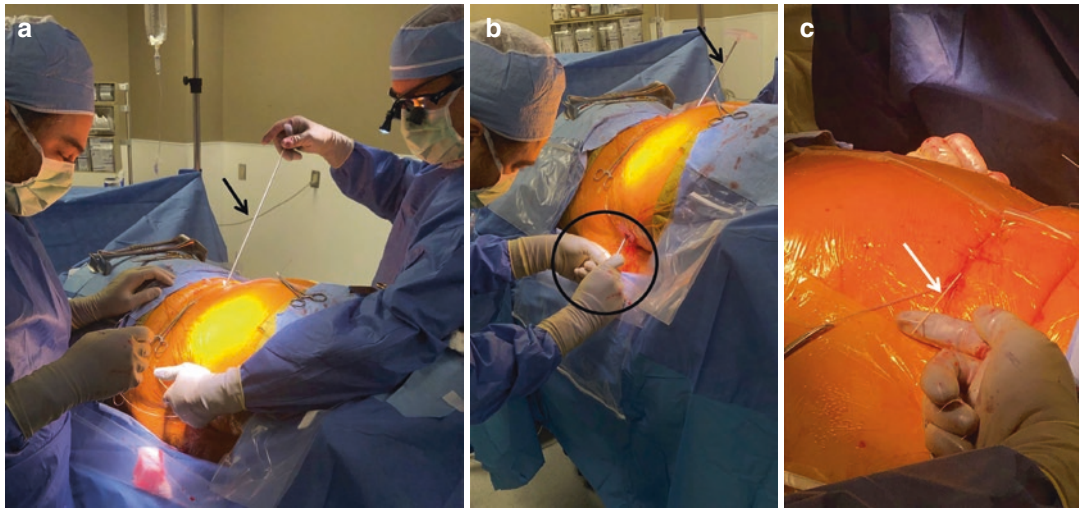

Fig. 20 (**a**–**c**) The malleable tunneling device (black arrows in **a** and **b**) is passed from the pump pocket superiorly to the more inferiorly located paramedian spine incision where the catheter placement has been performed. The catheter is then placed into the distal end of the tunneling device (indicated by black circle in **b**) and external portion of the catheter is advanced completely into the tunneling device. The tunneling device is then removed leaving only the catheter extending out of the pump pocket (white arrow in **c**). The flow of CSF out of the end of the catheter can be checked at this time to ensure patency

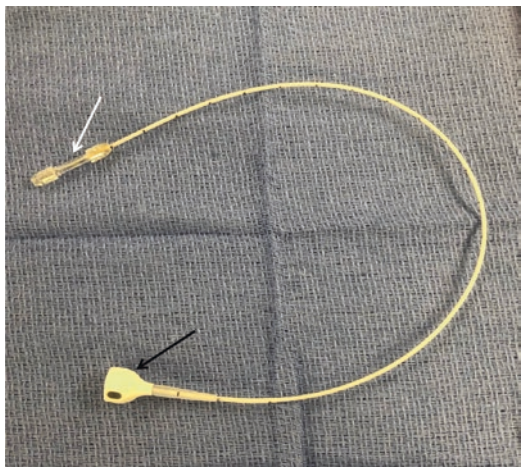

Fig. 21 Proximal catheter attachment that includes the collet (white arrow) that attaches to the remainder of the intrathecal catheter and the catheter attachment mechanism that attaches to the intrathecal pump (black arrow)

2011), it has not yet shown efficacy in decreasing infections in patients after intrathecal pump placement but can be used in this way to at the discretion of the implanting physician to keep the infection rate as low as possible.

Vancomycin powder, usually in a dose of 1 g, can be added to the wound and has been shown to be effective against Gram-positive bacterial strains in patients undergoing intrathecal pump placement (Ghobrial et al. 2014). It has also been shown to be safe in surgical procedures and has an additive beneficial effect in reducing surgical site infections when applied in addition to standard antibiotic prophylaxis (Abdullah et al. 2016). Most of the known side effects seen with intravenous administration do not occur when the drug is placed topically into a surgical wound, and there is little evidence that the routine use of topical vancomycin powder leads to antibiotic resistance. Routine use of vancomycin powder is supported by the existing literature and can be used as an adjunct prophylaxis against infection.

3.8 Closure of Incisions

Following irrigation and the topical antimicrobial measures have been applied the pump pocket and catheter insertion site are ready to be closed. Both incisions are typically addressed with a layered closure starting with a resorbable suture

such as a 2-0 Vicryl suture placed in the deep tissues. The Vicryl sutures will typically resorb in 56–70 days and are effective for closing both the deep tissue and the skin using a subcuticular suturing technique. The paramedian spinal incision is typically small enough to be closed using Vicryl suture alone. A single deep suture is placed to close the deep fascia then an interrupted subcuticular closure is performed with Vicryl suture. The abdominal wound is usually larger and interrupted Vicryl sutures are used to close the deeper layer of Campers fascia followed by a superficial and skin closure using either interrupted Vicryl sutures or a unidirectional barbed resorbable suture such as V-loc™ or Stratafix. The unidirectional barbed sutures hold the tissue firm after passing through it and can therefore be placed using a running suture technique rather than as a locking suture which allows the surgeon to close the wound more expeditiously. If skin tension is a problem after the closure or if the skin edges are not tightly approximated, surgical staples can be used to reinforce the closure of the incision. A topical adhesive such as 2-octylcyanoacrylate (Dermabond) that sets in approximately 60 s can be added to the superficial portion of the incision along with a physical barrier such a Prineo mesh tape to allow the patient to shower immediately after they return home.

3.9 Post-Op Instructions

After the wounds are closed, the patient is taken to the recovery area where the pump can be programmed to deliver the prescribed amount of medication. It should be kept in mind that because the pump tubing and catheter are not filled with medication, a bridge bolus must be performed in order to clear the indwelling CFS and to immediately delivery the prescribed medication dose.

If the patient has had an adhesive barrier placed over the skin would closures, they are instructed that they can shower any time after returning home but bathing or other submersion of the wounds are prohibited until they are completely healed. The patient is instructed to wear an abdominal binder for 6 weeks until the incisions are healed and the pump stabilized along the anterior abdominal wall. It is important for the patient to be compliant with the binder as this will stabilize the pump and will facilitate it healing in the appropriate position and will lessen the chance that the pump does not become adherent to the abdominal wall and develops a loose pocket where the pump can flip or rotate. The patient is also instructed to limit such activities as bending at the waist, twisting, reaching, or other heavy physical activity to ensure the tissue around the pump heals optimally, and there is no movement in the position of the catheter.

4 Intrathecal Drug Delivery—Pump Management

4.1 Management of Intrathecal Pain Pumps

4.1.1 Patient Selection for IT Therapy

Modern literature supports utilizing IT therapy earlier as a functional therapy that has been shown to be efficacious and cost-effective rather than as a salvage therapy (Pope et al. 2015). Intrathecal therapy should ideally be used for refractory pain in patients who have undergone multiple clinically appropriate therapies that have not produced adequate relief of pain and improvement of function. Proposed algorithms have been suggested for selecting the appropriate treatment in patients that don't have cancer and are not at the end of life (Fig. 22) and for patients that are experiencing cancer-related pain (Fig. 23) (Deer et al. 2017).

There are portions of the algorithm that are especially important. As we have discussed, compared to systemic opioids IT opioids appear to be more effective, better tolerated, and safer (Centers for Disease Control (CDC) 2011). As the opioid use increased in the United States, the Center for Disease Control (CDC) drafted updated guidelines for pain control stressing nonpharmacological, non-opioid, and non-systemic treatments before resorting to systemic opioids (Centers for Disease Control n.d.). Intrathecal therapy plays

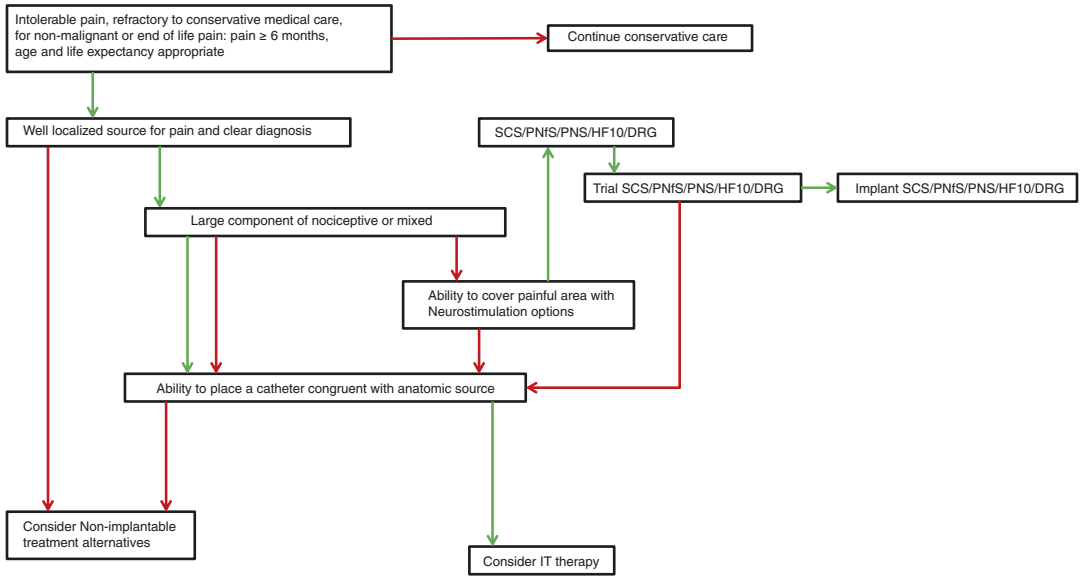

Fig. 22 Algorithm for placement within the pain care algorithm for non-cancer or non-end-of-life pain. *DRG* dorsal root ganglion, *HF10* high frequency stimulation, *PNfS* peripheral nerve field stimulation, *PNS* peripheral nerve stimulation, *SCS* spinal cord stimulation. Green arrows indicate an affirmation or positive response; red arrows signify a negative response. Adapted from: Deer TR, Pope JE, Hayek SM, Bux A, Buchser E, Eldabe S et al. The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines. Neuromodulation. 2017 Feb 1;20(2):96–132. https://doi.org/10.1111/ner.12538

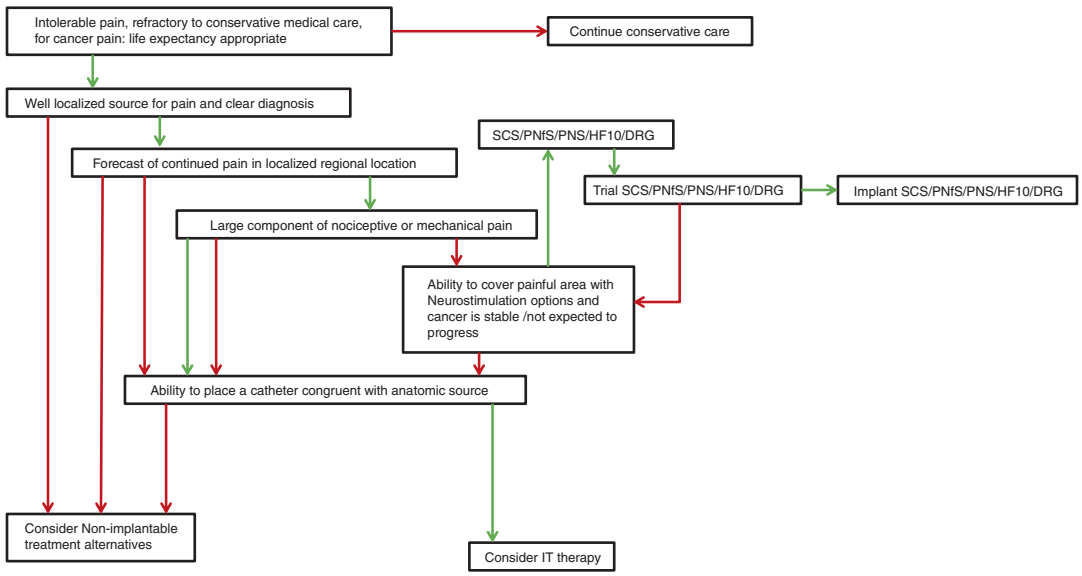

Fig. 23 Pain care algorithm for cancer-related pain. *DRG* dorsal root ganglion, *HF10* high frequency stimulation, *PNfS* peripheral nerve field stimulation, *PNS* Peripheral nerve stimulation, *SCS* spinal cord stimulation. Green arrows indicate an affirmation or positive response; red arrows signify a negative response. Adapted from: Deer TR, Pope JE, Hayek SM, Bux A, Buchser E, Eldabe S et al. The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines. Neuromodulation. 2017 Feb 1;20(2):96–132. https://doi.org/10.1111/ner.12538

an important role in this pain treatment continuum.

As noted in Fig. 22, IT therapy is the same level of therapy as neuromodulation, but it is generally recommended that if the patient's pain can be effectively treated with neuromodulation then that should be the first treatment that is offered (Coffey et al. 2010). Although traditional spinal cord stimulation (SCS) has been shown in multiple trials to be safe and effective (North et al. 2005; Kumar et al. 2006, 2007), there are a number of patients who become tolerant to the neurostimulation (Kumar et al. 2006) and the explant rate has been reported to be as high as 23.9% (Hayek and Veizi 2015). Given the durability of IT therapy (Saulino and Stearns 2015) and the relatively high loss of therapeutic coverage with SCS, there may also be a role for IT therapy before SCS in patients considered at high risk for loss of SCS therapeutic coverage.

The algorithm hierarchy for patients with cancer (Fig. 23) is similar to that of non-malignant pain. Intrathecal therapy has been shown to result in fewer side effects, better pain control, less mortality, and less costly as compared to conventional medical management (Smith et al. 2002; Staats et al. 2004; Stearns et al. 2016). As compared to SCS, IT therapy is also likely better for nociceptive pain and the medication can be continually titrated to effect which is easier for the patient than adding additional electrodes or repositioning the existing SCS electrodes. The life expectancy of the patient with cancer should be greater than 3 months for them to be considered a candidate for IT therapy.

4.1.2 IT Therapy in Different Pain States

Selection of the appropriate IT medication is based not only on the type of pain but on many features including the patient's age, life expectancy, location of pain, catheter location, and previous exposure to opioid medications. The pharmacokinetic spread of the medication used is also increased with bolus delivery as compared with a continuous infusion (Yaksh et al. 2017). Both nociceptive and neuropathic pain will respond to a number of pain medications but in patients with neuropathic pain, the medications most likely to be effective at treating this type of pain are ziconotide, opioids plus an anesthetic and an opioid or an anesthetic alone.

It should be kept in mind that increased medication concentrations and daily administrations of opioids can lead to granuloma formation and one should exercise caution not to rapidly escalate the dose or concentration of the medication as these are known factors associated with intrathecal granuloma formation (Deer and Pope 2015). One consideration when a malfunction of the IT delivery system is suspected is a catheter tip granuloma.

When deciding on the medications to use to treat neuropathic and nociceptive pain, the Polyanalgesic Consensus Conference (PACC) guidelines integrated their two sets of recommendations from 2012 and 2016 to arrive at recommendations to treat patients with cancer-related illness (Table 14) and non-cancer pain (Table 15) (Deer et al. 2017). The recommendations come in the form of tiered suggestions and one strategy that stands out is the earlier use of multiple medications in those patients with cancer-related pain as compared to their non-cancer-related counterparts. Typically, the uses of single, on-label agents are advocated for use initially and these are typically combined with other FDA-approved medications that have Level I data supporting their use. If the patient does not respond optimally well with the single agent therapy, then hydromorphone or a combination of medications including bupivacaine may be used (Tables 14 and 15). Additional agents can be combined with the initial medications and including such additional drugs as fentanyl, ziconotide, clonidine, and sufentanil. Baclofen may also be utilized, as it can be helpful in managing pain associated with spasticity.

A predictable dose–response medication characteristic is also desirable but care should be taken not to increase the medication above the recommended levels (Deer et al. 2012a). The tiered hierarchy of medications recommended for use for patients with certain types of pain was based on the levels of evidence of the safety and

Table 14 Cancer or other terminal condition-related pain with diffuse nociceptive or neuropathic pain

Line 1A	Ziconotide			Morphine		
Line 1B	Hydromorphone			Morphine or Hydromorphone + Bupivacaine		
Line 2	Hydromorphone or Morphine + Clonidine			Morphine or Hydromorphone + Ziconotide		
Line 3	Hydromorphone or Morphine or Fentanyl + Bupivacaine + Clonidine	Ziconotide + Bupivacaine	Ziconotide + Clonidine	Hydromorphone or Morphine or Fentanyl + Bupivacaine + Ziconotide	Sufentanil	
Line 4	Sufentanil + Ziconotide	Baclofen	Sufentanil + Bupivacaine	Sufentanil + Clonidine	Bupivacaine + Clonidine + Ziconotide	Bupivacaine + Clonidine
Line 5	Sufentanil + Bupivacaine + Clonidine		Sufentanil + Bupivacaine + Ziconotide		Sufentanil + Clonidine + Ziconotide	
Line 6	Opioid[a] + Bupivacaine + Clonidine + Adjuvants[b]					

Adapted from: Deer TR, Pope JE, Hayek SM, Bux A, Buchser E, Eldabe S et al. The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines. Neuromodulation. 2017 Feb 1;20(2):96–132. https://doi.org/10.1111/ner.12538

[a]Opioid (all known intrathecal opioids)

[b]Adjuvants include midazolam, ketamine, octreotide

efficacy associated with the use of those medications. The combination of an opioid and bupivacaine and ziconotide used as a single agent both have Level I evidence supporting their use in the cancer patient population (Smith et al. 2002; Staats et al. 2004). In contrast to bupivacaine, however, there little to no evidence that shows ziconotide is helpful when combined with opioids to help patients' with cancer-related pain as these studies have not yet been performed. Ziconotide combined with bupivacaine also has almost no supportive evidence. On the other hand, ziconotide has strong evidence for clinical efficacy and is very safe having no reported deaths or intrathecal granuloma formation from its use. Due to this level of evidence and a good safety record, the PACC guidelines state that ziconotide should be the first or one of the first drugs selected for treatment of patients with non-malignant pain (Deer et al. 2017).

When medications are mixed, the combination of the agents should trigger a concern for constancy of the amalgam and mixtures should be used only when they have been tested for stability (Shields et al. 2008). The characteristics of the mixture are important for safety and efficacy of patient treatment but are also important for stability within the pump itself as at least one

Table 15 Non-cancer-related pain with diffuse nociceptive or neuropathic pain

Line 1A	Morphine		Ziconotide[a]	
Line 1B	Hydromorphone		Morphine or Hydromorphone + Bupivacaine	
Line 3	Hydromorphone or Morphine + Clonidine		Fentanyl + Bupivacaine	Ziconotide + Morphine or Hydromorphone
Line 4	Hydromorphone or Morphine + Bupivacaine + Clonidine	Fentanyl + Ziconotide	Sufentanil + Bupivacaine or Clonidine	Ziconotide + Clonidine or Bupivacaine or Both
Line 5	Fentanyl or Sufentanil + Bupivacaine + Clonidine		Sufentanil + Ziconotide	Baclofen
Line 6	Opioid + Ziconotide + Bupivacaine or Clonidine			

Adapted from: Deer TR, Pope JE, Hayek SM, Bux A, Buchser E, Eldabe S et al. The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines. Neuromodulation. 2017 Feb 1;20(2):96–132. https://doi.org/10.1111/ner.12538

[a]Ziconotide should be first choice in patients with >120 morphine equivalents or fast systemic dose escalation, in the absence of history of psychosis

medication has been reported to lead to corrosion of the pump motor (Medtronic PLC n.d.).

If mixing of medications is done, it is important to remember that the patient may need to be weaned off the primary medication prior to changing to a different single medication or to mixing in new medications. In addition to opioids, medications associated with significant withdrawal syndromes include baclofen and clonidine and these medications require a strategy for treating withdrawal when changing from these to other medications. In contrast with these medications, ziconotide and bupivacaine do not have a risk of withdrawal and can be stopped abruptly without undue risk.

4.1.3 Starting Doses and Bolus Dosing

Most recommended starting doses assume a continuous infusion rather that a bolus-type administration. The starting doses can vary greatly according to the patient's baseline oral opioid intake and their underlying medical conditions, especially those that involve compromise of the respiratory system. Overall, recommendations on starting doses are very conservative and start low with slow increases of the IT medications. This is done to maximize the safety of opioid medication administration. Trialing of IT medications has been discussed above, and it has been reported that expert consensus supports initiation of the continuous medication dose after implantation be half of the successful trialing dose (Deer et al. 2017).

Typically for patients starting IT therapy after pump implantation, they are given a baseline dose that is approximately half of the successful trial dose as stated previously but are also given the ability to give themselves additional controlled boluses of medication. This is

known as patient-controlled bolus administration and is called a myPTM™ Personal Therapy Manager when this technique is used through the SynchroMed II IT pump. The PACC recommendations support a bolus dosage of between 5 and 20% of the total daily dosage. There is also evidence that up to 30% of the total daily dosage can be given as a bolus dose up to four times daily (Ando et al. 2011). The bolus strategy may be used to allow the patient to treat their pain as needed in a controlled manner and when they present for a titration of their baseline dose the functional dose that they have been receiving which is the combination of their baseline dose plus their bolus usage will have been shown to be a safe dosage of medication. Their baseline can then be turned up to that total dose safely and the patient cautioned not to use their bolus doses until they determine the adequacy of the baseline dose for controlling their pain. The goal of this method of dose titration is to arrive at a good stable baseline dose that controls the patient's pain while preserving the ability to give additional doses of medication when needed.

Maximum recommended daily doses of medications are primarily based on animal and clinical studies. Fentanyl and Sufentanil are well tolerated and, according to animal studies, these medications can be given at very high doses without signs of neurotoxicity. Despite this most experts avoid giving very high doses chronically due to the risk of developing OIH and because of the high plasma levels of the medication resulting from the high CSF doses may limit the advantages of intrathecal therapy by allowing it to cross over to become a systemic therapy (Deer et al. 2017). Most experts also feel that doses higher than 1000 mcg of fentanyl or of 500 mcg of sufentanil are not beneficial and that the lowest possible concentration of these medications should be used as higher doses and higher concentrations may have diminishing benefits. At doses higher than 1000 mcg, the lipophilic nature of these medications may allow systemic exposure as high as those seen with transdermal use. In general, although doses higher than 1000 mcg per day of fentanyl can be used, this dose should serve a benchmark for re-evaluation of the efficacy of the existing therapy.

Table 16 Maximum concentrations and daily doses of intrathecal agents

Drug	Maximum concentration	Maximum dose per day
Morphine	20 mg/mL	15 mg
Hydromorphone	15 mg/mL	10 mg
Fentanyl	10 mg/mL	1000 mcg
Sufentanil	5 mg/mL	500 mcg
Bupivacaine	30 mg/mL	15–20 mg[a]
Clonidine	1000 mcg/mL	600 mcg
Ziconotide	100 mcg/mL	19.2 mcg

Adapted from: Deer TR, Pope JE, Hayek SM, Bux A, Buchser E, Eldabe S et al. The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines. Neuromodulation. 2017 Feb 1;20(2):96–132. https://doi.org/10.1111/ner.12538

[a]May be exceeded in end-of-life care and complicated cases as determined by medical necessity

Bupivacaine is similar to Fentanyl and Sufentanil in that higher doses are well tolerated (Veizi et al. 2011). For the other intrathecal drugs, there are recommended maximum concentration and maximum recommended daily doses (Table 16).

4.1.4 Compounding of Intrathecal Drugs

The use of on-label non-compounded medications is typically the first-line recommendation and these medications have undergone extensive testing and an application to the FDA that involves showing adequate safety and efficacy of the medication. The production of these medications is evaluated on an on-going basis to ensure that high quality standards are met (Gudeman et al. 2013). In addition to the FDA-approved medications for IT use, there remains a need for custom mixtures and formulation of medications that are not currently available for clinical use. The practice of mixing medications together is called pharmacy compounding. This process is not FDA regulated but is regulated by the state pharmacy boards (Gudeman et al. 2013).

Due to the lack of regulation by the FDA, the quality of the medication mixture and the quality control measures of each of the compounding

pharmacies are of paramount importance. These pharmacies combine and mix various types of medication into a mixture keeping track of various aspects of the mixture including the concentrations of each medication, the compatibility of the different drugs and the overall pH of the solution. If the physician decides to use a compounding pharmacy to provide some of the off-label medications to patients, he/she should be cognizant of the quality control measures of the specific pharmacy.

The manipulation of sterile products using sterile conditions is classified as low-risk compounding. This includes the dilution of sterile on-label IT medications such as Mitigo (Piramal Critical Care, Inc., Bethlehem, PA, USA), but combining any sterile solution with a powder formulation (i.e., bupivacaine) could alter the classification to high-risk compounding.

There has been substantial debate and discussion about the risks and utility of compounding medications for IT medication therapy (Gudeman et al. 2013; Ghafoor et al. 2007). This includes the use of off-label medications as well as dilution of on-label medications. It is generally thought that the traditional limited number of on-label medications and the need for additional clinical efficacy has driven the use of IT-compounded medications. The previous comments by the PACC recognized the risks associated with IT medication compounding and distinguished certain important components that go into ensuring optimal quality including adequate quality assurance programs, sterile air processing, and regular calibration of the equipment (Deer et al. 2012a).

In the past, one manufacturer reported the presence of corrosion on a certain component of the pump due to the use of a compounded medication that lead to the failure of the infusion system (Medtronic's SynchroMed II Infusion System 2012). When examined objectively the stall rate for the SynchroMed pumps was reported as 2.4% when on-label medications were used and 4.5% when off-label medications were used (Rezai et al. 2013). Despite the increased stall rate, the PACC stated that compounded IT medications were an acceptable standard of care and that adequate peer-reviewed literature exists to support the use of compounded as well as non-compounded medications (Deer et al. 2012a).

The concentration of the medications used for IT delivery is also very important as lower concentrations can contribute to stability of the medication and high concentrations can allow for a longer interval between pump refills. Changes in concentration can alter the pH of the drug solution, which can lead to precipitation of the medication and subsequent failure of the catheter or the pump and recurrence of the patient's symptoms (Kim 2011; Medtronic 2009). Currently, most physicians use some IT medications that have some degree of manipulation or are off-label so it must be known that these medications are associated with a slightly higher pump stall rate and a slightly higher rate of medication issues.

4.1.5 Intrathecal Medication Combinations

Combinations of medications for IT use is common and the majority of the safety testing for the various types of drug combinations have involved morphine combined with other medications. Some of the medications studied with morphine include bupivacaine, baclofen, and ziconotide (Mercadante et al. 2007). It has been found in multiple studies in patients with both cancer and non-cancer-related pain that combining bupivacaine with morphine is significantly more effective than morphine used alone (Krames 2012; Raffaeli et al. 2008). In another study of 25 patients on IT ziconotide, morphine was added which improved their pain scores by an average of 26.3% and decreased their systemic opioid dose by 49.1% (Webster et al. 2008).

4.1.6 Training and Educational Qualifications for Physicians Implanting and Managing Intrathecal Medication Therapy

There has been rapid growth of knowledge dealing with the implantation and management of IT pumps. In addition to the increased body of knowledge relative to the pharmacology and clinical management, there has also been an increase

in the commercially available intrathecal pumps. While this chapter only covers Medtronic's SynchroMed II pump, other pumps may have variations in their propellant mechanisms, their MRI compatibility and their specific engineering limitations. The fast-paced clinical knowledge combined with changing pump technology emphasized the need for updated and optimal training of providers that implant and manage IT pumps.

The specific training and educational elements depends upon the scope of practice for the particular provider and the type of patients being treated. The training may be provided by formal academically sponsored programs, industry-related courses or by instructional cadaver labs. The credentialing for the management and procedural aspects of IT therapies is left to the discretion of the hospital or treating facility.

A distinct shortcoming of providers of all types is the general lack of understanding and knowledge related to IT therapy. All providers should have at least a basic working knowledge of what an IT pump and catheter system is and what conditions it is used to treat. They should also be able to distinguish an IT pump from a neurostimulator or a cardiac pacemaker, as these are very different systems with different applications. Part of the knowledge base needed is how to appropriately triage a patient with an indwelling pump to a qualified pump manager or an appropriate manufacturer representative. This training should begin in medical school and should continue with continuing medical education (CME). Unfortunately, no training of this kind exists anywhere in the countries where IT pumps are utilized.

When a patient is admitted to a hospital or healthcare facility, they should have their pump information on hand including the type of pump, pump manufacturer, estimated replacement interval, medication, dosage, dosing regimen, and refill date available. This information is routinely available on a printout that is given to the patient at the time of their last pump refill. If the printout is not available, it will require an electronic interrogation by qualified personnel to determine the existing pump and medication parameters. This information can then be entered as part of their medical record. Appropriate documentation of the pump type and manufacturer needs to be performed prior to proceeding with elective surgery or performing an MRI.

The credentialing for pump managers and pump implanters will vary according to the facility but some education including lectures on pumps and neurostimulators and on the electronic interrogation for both. Some institutions recommend a minimum of ten electronic device interrogations per year to maintain their credentials and 20 supervised pump refills prior to a physician surrogate performing refills independently. It is the recommendation of the most recent PACC guidelines that each accredited facility have the ability to evaluate an indwelling implantable pump and catheter system (Deer et al. 2017).

Nearly all patients with an implanted IT pump will require pump interrogations and refills on a regular basis. The provider that performs the interrogations and refills may either be a physician or a non-physician provider under the supervision of a managing physician. Whomever provides these services it is expected that they will have been appropriately trained to perform these duties which, in addition to electronic analysis and pump refills, will include detection of a refill outside the pump reservoir (pocket fill), identifying residual volume discrepancies, being able to recognize symptoms of over/underdosing or granuloma formation, and knowing which medications are appropriate for IT use and the pharmacology associated with these medications. It is also expected that the pump manager will be able to perform catheter and rotor studies (see Sect. 5.1) to establish the proper diagnosis when a pump or catheter malfunction is suspected. There should always be an appropriately educated and credentialed physician who either performs these duties or supervises them. A common recommendation is a minimum of ten pump refills per year be performed so that the individual performing these refills maintains adequate competency. If this minimum cannot be maintained, the most recent PACC guidelines recommend that the refill

should be directly supervised or performed by the physician pump manager or by a manufacturer representative (Deer et al. 2017).

In regard to physicians performing pump and catheter implantations, it is generally considered a surgical procedure that requires basic surgical skill to perform the procedure safely. There are physicians who implant the pump but don't manage and vice versa, but there are a few physicians that do both implantation and management. In the situation where the pump manager and implanter are not the same person, close communication should occur so the correct medication is used and the appropriate pump position and catheter tip level is known. A pump should also never be placed unless there is a qualified provider available to manage the pump and appropriate post-surgical follow-up has been arranged to ensure optimal wound healing and to look out for signs of adverse effects of the IT medication. If the pump has to be explanted, the pump manager must communicate to the explanting physician the strategy moving forward including post-op patient monitoring and the correct systemic replacement medication that is to be used.

The implanting physician should have training in the area of pain medicine, interventional radiology, or surgery and must be able to appropriately place the pump (see Sect. 3.5) and to tunnel a catheter from the catheter insertion site to the pump site (see Sect. 3.6). The implanting physician should also be facile with diagnosing and treating intraoperative surgical complications and postoperative complications related to IT medication delivery. It is fairly common for institutions to require anywhere from two to ten pump implants performed under the supervision of a credentialed implanter before the physician is able to independently perform these implantations and another two to five implants every 2 years are commonly required to maintain clinical competency.

If the managing physician and implanting physician is the same individual, it is expected that they will meet all of the knowledge, educational, and training requirements listed above. When training on a certain device is not available from a physician peer, then assistance from the device manufacturer is appropriate. It is well recognized that the training to manage an intrathecal pump is very important to the longstanding success of the therapy and all pump management physicians should have adequate and continuing educational training that includes information related to all current FDA-approved devices.

4.1.7 Continuation of Effective Intrathecal Opioid Therapy

In 2002, the results of a randomized control trial (RCT) comparing comprehensive medical management to TDD for the treatment of cancer-related pain (Smith et al. 2002). This study demonstrated that TDD improved clinical success in treating pain, decreasing drug-related toxicities and in improving survival. Results of three prospective 3-year follow-up studies of patients who were treated with low dose intrathecal opioids were published in 2012, 2015, and 2016 (Hamza et al. 2012, 2015; Grider et al. 2016) and demonstrated that conversion to IT opioid therapy, discontinuation of systemic opioid use, and maintenance on low doses of IT opioids can be effectively used to treat chronic pain. A manuscript published in 2014 recounted the best IT therapy practice recommendations by 12 experienced pain management practitioners who concluded that TDD is a valuable alternative drug delivery system for patients with severe pain (Prager et al. 2014).

Many chronic pain patients tend to get less pain relief and develop more medication tolerance over time with systemic agents and are subject to the risk of opioid-related side effects or overdose. Changing the route of delivery reduces these side effects and lessens the chance of an overdose (Smith et al. 2002; Dunn et al. 2010). Changing the route of deliver also mitigates the development of tolerance to the opioid medications. This route change is reasonably common after pump implantation. The National Outcomes Registry for Low Back Pain reported data on 72 patients that received a pump implant and were available for a 1-year follow-up and found that at 6 months 65% of the patients had decreased or stopped their use of systemic opioids and at

12 months 42% of the patients had done so (Deer et al. 2004). In 2013, Caraway et al. reported a retrospective study of 99 patients that showed systemic opioids were required by 90% of this patient cohort before the pump implantation and only 16% required them at 1 year following the implant (Caraway and Hinnenthal 2013). Intermittent increases in pain are treated with the myPTM® Personal Therapy Manager (Medtronic Inc., Minneapolis, MN) which provides patient activated dosing capability that is set under the boundaries of the managing physician.

It is generally thought that once patients have made the decision to transition to IT opioid therapy they should be weaned off systemic opioids either before or after pump implantation. This is typically done to propagate the optimal efficacy of the final IT therapy. This strategy takes advantage of the opioid metabolism pathways to optimize the amount of pain relief a patient receives.

4.1.8 Opioid Tolerance and Its Effect on IT Opioid Therapy

Although opioids differ somewhat in how they are metabolized, there are several patterns of metabolism that are well defined. Most opioids are metabolized extensively in the liver before entering into the systemic circulation. The portal venous system carries blood primarily from the gastrointestinal (GI) tract and accounts for approximately 75% of the blood flow to the liver. When opioids are ingested, they are absorbed in the GI tract and are carried to the liver where they are metabolized. The metabolism takes a typically lipophilic opioid and makes it more hydrophilic in order to facilitate its excretion in the urine.

Opioid metabolism primarily occurs in the liver in two phases. Phase 1 involves the cytochrome P450 (CYP) enzymes that modify the opioid and Phase 2 conjugates the product making it hydrophilic and easily excreted. The degree of upregulation of the CYP enzymes can be profound. In addition to the role of CYP in mediating opioids, the biotransformation processes also contribute to opioid tolerances secondary to induced enzymatic expression (Berkowitz 1976; Säwe 1986).

The result of this is that the blood supply that drains the bowel contains high concentrations of opioids that flood the liver and the CYP enzymes and contribute to upregulation and tolerance. Prior to statutory regulation of maximum opioid doses, our practices saw patients on doses of a few hundred milligram equivalents of morphine or more and occasionally saw patient referred in for TDD that were consuming more than 1000 mg equivalents of morphine daily. Typically, we would use the 1:100 ratio when calculating the intrathecal to oral equivalent dose in a patient that is opioid tolerant but doses in excess of 5.0 mg of intrathecal morphine prompted caution and reconsideration of the appropriate dose. After some ineffective and under-dosed trials, doses higher than 5.0 mg of IT morphine were given to patients on an excess of 500 mg equivalents of morphine daily and doses up to 8.0 mg were occasionally given for those patients on exceedingly high doses.

Although we were prepared for an opioid overdose what was seen nearly every time is a prominent decrease in the amount of the patients pain of 80% or greater followed by a prompt reappearance of the pain within 3–6 h and a return of the patients' condition to their baseline. This scenario was relatively common in patients on very high doses of opioids and emphasized to us the incredible ability for the CYP system to upregulate to the point that there is almost no amount of opioid that can be given intrathecally that can treat pain in an extremely tolerant and upregulated patient that continues on oral or transdermal medications. Due to the almost infinite amount of upregulation that is seen in the liver and due to the inevitable OIH that is seen in patients on chronic narcotics, we do not allow any systemic narcotics for more than 2 weeks after pump implantation as the systemic narcotics will almost certainly be a self-defeating therapy when attempting to manage a patient's chronic pain.

4.1.9 IT and Systemic Medication Strategies

In addition to no oral or transdermal medications, we typically use branded medications prior to

switching to or adding compounded medications but compounded medications can be effective and comparable to their branded counterparts. An investigation by Rosen et al. comparing compounded morphine with branded intrathecal morphine found no significant differences in dose accuracy and device-related safety events and an additional study by Deer found no difference in rates of catheter tip granulomas between the two types of medications (Rosen et al. 2013; Deer 2004). Rosen et al. found a significantly better pain and functional improvements with the compounded medication while the branded medication showed significantly better results in pain reduction only (Rosen et al. 2013). This could certainly have been attributed to the significantly higher dose of morphine seen in the patients with compounded medication, which was given to this patient cohort only after failure of a branded medication.

After implantation of the pump, any existing systemic opioid medication is cut in half weekly until the patient is completely off all oral and/or transdermal opioids. Although many opioid tapering protocols exist, our regimen is to reduce the systemic dose by half before the IT trial and to reduce it by half again prior to pump implantation. This strategy is an attempt to maximize the effectiveness of the trial and of the initial TDD therapy. There have been studies of different pre-implant and post-implant systemic opioid management practices. A report of 61 patients with a 3-year follow-up used a protocol where the systemic daily opioids were eliminated before the implant and restricted following the placement of the pump (Hamza et al. 2012). The patients were gradually weaned off half of their oral opioid medications over the course of 3–5 weeks before their trial. Following their trial, they were weaned off all of their opioids over the course of another 3–5 weeks and remained off of all oral opioid medications for 7–10 days prior to pump implantation. In this patient population, their IT opioid dose was 1.4 mg equivalents of morphine and remained almost constant for the next 3 years. Daily oral opioids were not used on a daily basis in this patient cohort. The authors thought that this gave them a sense of control to allow intermittent use of opioids similar to that found in patients who have access to their myPTM system (see Sect. 4.1, Starting Doses and Bolus Dosing) (Ilias et al. 2008; Maeyaert et al. 2003). The patients in this 3-year study experienced significant improvements in their pain, function and mood, which persisted throughout the study.

An additional study of 22 patients reduces their opioid intake over the course of time culminating in a 5-week opioid-free time period before their trial (Grider et al. 2011). After the trial, the patients remained off all systemic opioids for another 2 weeks prior to implantation and were kept systemic opioid free thereafter. One year after implantation, the mean VAS score was significantly lower, and their function had improved even on very low doses of IT opioids ranging in the microgram level with a dose–response relationship for effective analgesia of less than 0.4 mg of IT morphine.

A study by Hathaway et al. compared healthcare expenditures over a 1-year time period for chronic pain patients with implanted IT pumps that either eliminated or continued their systemic opioids after implantation (Hatheway et al. 2015). They concluded that more than half of the patients were able to completely eliminate their systemic opioids and that this elimination resulted in a 10–17% decrease in yearly expenditures.

Taken together the studies above show that opioid decrease or elimination before and even after pump implantation not only improves the patient's outcomes but it also likely results in a final lower effective pump dose and less costly long-term expenditures. Previous experience also shows that this can be accomplished in a variety of patients with chronic pain from different etiologies.

4.1.10 Sustainability of IT Opioid Therapy

One of the primary concerns of chronic IT opioid therapy is the potential for dose escalation over time. A retrospective study in cancer patients receiving IT opioid therapy for more than 3 months after attaining an initial stabilization dose showed that about half of these patients had their dosage increased to more than double the

initial stabilizing dose (4.8 mg of morphine per day) within the next 3 months (Yaksh and Onofrio 1987).

Another investigation of 52 patients undergoing IT opioid therapy for cancer-related pain demonstrated an increase in dose of 2.5 times the initial stabilizing dose of 3.8 mg per day within 4 months of therapy (Onofrio and Yaksh 1990). In a slightly longer term study of 50 cancer patients, investigators saw the mean daily dose of morphine increase from 2.5 to 9.0 mg in a time period averaging 142 days (Gestin et al. 1997).

Dose escalation is an even more important concern in patients receiving IT therapy for non-malignant pain as the overall duration of therapy is very likely to be longer than in patients with malignancy-related pain. In a large series of patients with non-malignant pain, investigators found that the mean IT morphine dose increased from 10 mg per day at 6 months following therapy initiation to 15 mg per day at 36 months (Roberts et al. 2001).

Different conditions may also have different propensities for dose escalation. In a study of patients with non-malignant pain, the presence of neuropathic pain was strongly associated with increased dose escalation (Mekhail et al. 2014). Another factor that is related to a greater chance of dose escalation includes IT therapy in patients less than 50 years old (Hayek et al. 2011b).

There are strategies to mitigate dose escalation. These includes decreasing the systemic opioid dose prior to performing an IT trial or pump implantation, slowly increasing the baseline dose, and using non-opioid medications such as bupivacaine, baclofen, and clonidine. Bupivacaine has been shown to have a synergistic interaction with opioids and authors have previously reported a mitigation of opioid dose escalation with the concurrent IT use of bupivacaine (Veizi et al. 2011; Maves and Gebhart 1992; Penning and Yaksh 1992).

In our practice, we characteristically begin with a branded opioid as monotherapy. Typically, this is IT morphine that is titrated to effect by using a baseline dose along the use of intermittent patient-controlled bolus dosing (myPTM™). At the follow-up visits, the pump data is analyzed to determine how many daily boluses the patient is using and the baseline dose is turned up to the combination of the existing baseline dose plus the sum of all of the daily bolus doses. The patient is then clearly informed that their dose has been increased and to use the boluses only when needed. This process is repeated until the patient achieves adequate pain relief or until the daily dose nears or reached 10 mg of morphine daily. If that dosage level is reached, additional medications are ordered and a compounded mixture typically consisting of an additional opioid (hydromorphone), an anesthetic (bupivacaine), and an alpha-2 adrenergic agonist and anti-inflammatory (clonidine) is introduced and the morphine dose reduced by half. The process is repeated with intermittent increases of the baseline dose until a total daily dose reached 20 mg equivalents of morphine, then the dose is slowly decreased back down to a little as 5 mg equivalents of morphine daily and then slowly titrated to effect after that. This strategy will help mitigate against the steady dose escalation often seen in patients on chronic IT opioid therapy and can keep the overall daily dose at a level that will not be catastrophic if there is a failure of the pump or catheter and a dose that can be treated with oral rescue medications if the IT dosing suddenly stops.

4.2 Management of Intrathecal Baclofen Pumps

The goals or potential goals in the management of spasticity include treatment that will decrease spasticity and the pain associate with it and to improve the patient's functional ability and independence. If effective treatment is not rendered, excessive muscle tone can cause pain, stiffness, decreased range of movement (ROM) and deformity that can significantly impair the patient's quality of life. The goals also include more immediate benefits such as improved ambulation, greater ease of rehabilitation therapy, and better hygiene as well as long-term goals including the prevention or the limitation of the incidence of joint contractures. Decreasing spasticity can also

help the caregiver in saving time and making their care regimen more effective.

Spasticity can be either focal or generalized. Focal spasticity has typically been treated with chemodenervation (botulinum neurotoxin type A) (Simpson et al. 2008; Esquenazi et al. 2013). This treatment is generally very effective but is temporary and may not be adequate for controlling spasms over a long period of time or in patients with multifocal or severe spasticity.

The management of severe spasticity typically requires a comprehensive approach including physical therapy and rehabilitation techniques and pharmacological treatments (Thibaut et al. 2013; Bakheit 2012). Many oral medications for spasticity have been utilized, but baclofen is one that has been the most commonly employed medication used to treat this condition (Lance 1980). Despite the efficacy of the medication in patients with mild or even moderate spasticity, oral baclofen can produce less than optimal results or can cause unacceptable side effects at doses that are therapeutic for patients with more severe spasticity (Lance 1980; Alexon 2005).

Intrathecal baclofen (ITB) therapy is useful when oral baclofen is inadequate and is indicated for use in patients with severe, chronic spasticity of spinal or cerebral origin. This includes the use of ITB for the conditions described in Sect. 1.2. The effectiveness of ITB for controlling spasticity has been shown in controlled studies in cerebral palsy, multiple sclerosis, spinal cord injury, and stroke (Ertzgaard et al. 2017).

Baclofen delivered directly into the cerebrospinal fluid (CSF) can be an alternative to oral medication as the intrathecal delivery bypasses the blood–brain barrier (BBB) entirely. This method of delivery allows much lower doses to be administrated as it is delivered directly to the neural axis where the CSF concentration is much higher than the plasma concentration, and it has been determined that the ITB does is typically one hundred to one thousand times smaller than the comparable oral dose (Barnes and Johnson 2008). This allows for the lower dose to be much more effective and limits the CNS side effects of baclofen such as drowsiness, headaches, or sedation (Meythaler et al. 2001). Intrathecal baclofen therapy can be used alone or in conjunction with other methods of managing spasticity described above and, often, the therapeutic strategy includes the use of multiple treatment options used together (Fig. 24). The therapies were traditionally tried in a hierarchical manner starting with simple things first such as the removal of noxious stimuli followed by physical therapy, oral medications, and then ending up with chemodenervation and ITB therapy (Fig. 25). Surgery remained an option in very refractory cases where ITB therapy may be incompletely effective (Fig. 25). Typically, the therapies are used in a synergistic manner and may be used concurrently as shown in Fig. 24.

Baclofen is an optimal medication for intrathecal delivery as it is slightly lipid soluble and remains in the CSF after ITB administration and has a relatively long half-live for a medication of 90 min (Hsieh and Penn 2006). In the intrathecal space, there is a gradient in drug distribution between the cephalad and caudal portions of the spinal cord with a 4:1 concentration differential that is greater in the spinal and cauda equina region than it is in the brain (Kroin and Penn 1991). In addition to making the medication more effective on the lower extremities than the brain, the concentration differential also serves to decrease side effects (Kroin and Penn 1991). There are also animal studies showing a prominent gradient of baclofen during slow infusion so that most of the ITB remains around the catheter tip (Bernards 2006). The implication of this is that the catheter tip position is important in determining the clinical efficacy for the patient's specific condition. An example of this was shown by Grabb et al. when they determined that the placement of the tip of the intrathecal catheter at the T6-7 level was associated with greater relief of upper extremity spasticity that the same dosages administered at the T11-12 level without the loss of effect on the lower extremities (Grabb et al. 1999).

The contraindications for ITB therapy are divided into absolute and relative contraindications with the absolute contraindications including a hypersensitivity to baclofen (rare); the patient's body habitus precludes pump

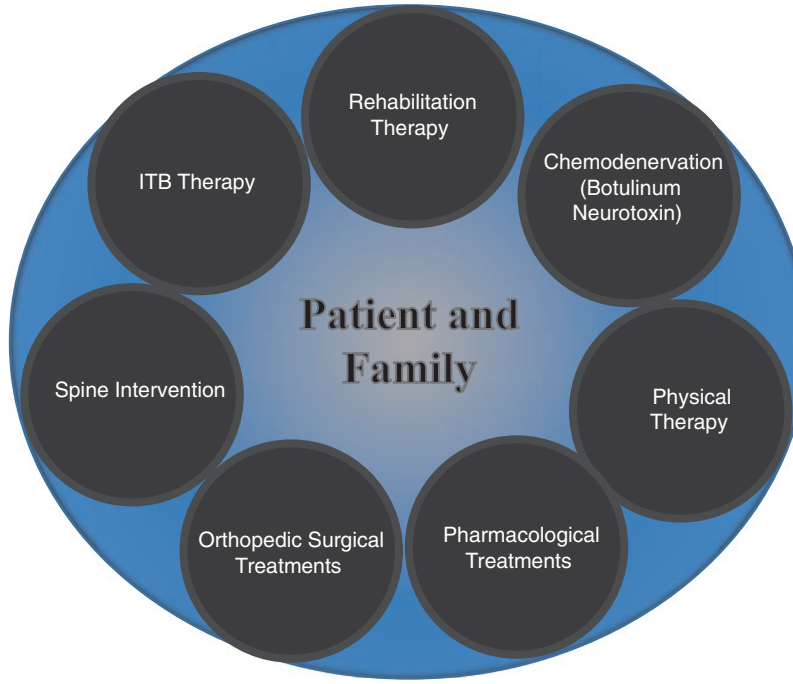

Fig. 24 The use of intrathecal baclofen therapy is typically in conjunction with other methods of managing spasticity. These methods are designed to work in a synergistic manner to positively affect the patient and their family

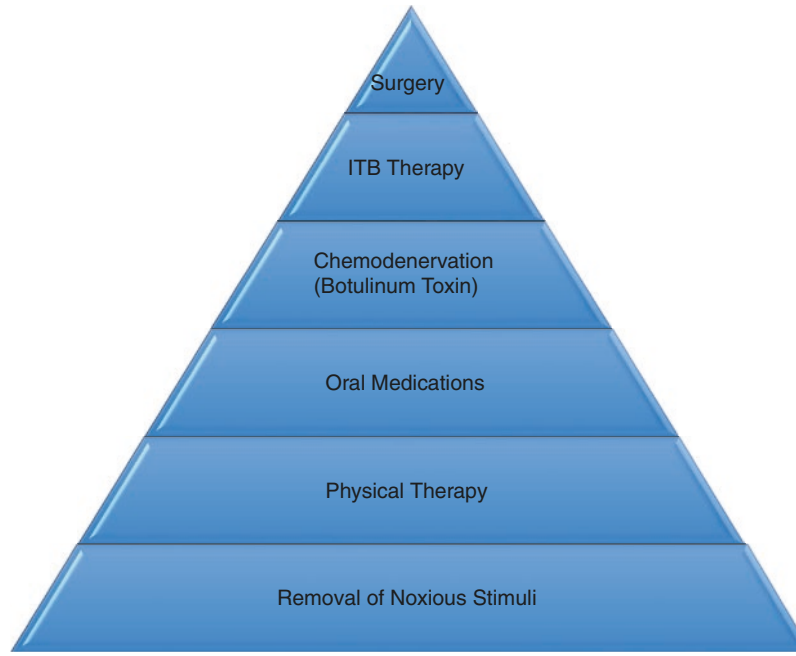

Fig. 25 The sequential model of spasticity management starting with simple things first such as the removal of noxious stimuli followed by physical therapy, oral medications and then ending up with chemodenervation, ITB therapy and surgery

implantation and the presence of an active and untreated infection (Saulino et al. 2016). The relative contraindications include psychosocial factors or mental health issues precluding compliance, unrealistic patient goals, and undue financial burdens (Saulino et al. 2016). Additional items to consider prior to pump implantation or pump replacement surgery are whether the patient will be undergoing shunt surgery for hydrocephalus, whether they have

abdominopelvic or spine surgery planned and whether or not they have a seizure disorder. All of these factors can affect the timing or technique of placing an intrathecal pump and catheter.

5 Intrathecal Pump and Catheter Troubleshooting

Occasionally, a patient with a baclofen or pain pump will present with symptoms of medication withdrawal and a suspicion that the pump is not working properly. In the absence of hearing a pump alarm, the patient has no way of knowing for certain if the catheter and pump are still operating appropriately or not but they are likely to experience symptoms of medication withdrawal. In patients with baclofen pumps, these symptoms are likely to be increased spasticity, neuroleptic malignant syndrome, sepsis, serotonin syndrome, malignant hyperthermia, autonomic dysreflexia, seizure, and autonomic storming (Watve et al. 2012). Patients on IT opioid therapy can also have withdrawal symptoms following cessation of pump function. These symptoms can be divided into early and late symptoms. Early symptoms include agitation, muscle aches, restlessness, anxiety, increased tearing, runny nose, excessive sweating, inability to sleep, and yawning. Late symptoms include diarrhea, abdominal cramping, nausea and vomiting, skin, goose bumps, dilated pupils, rapid heartbeat, and high blood pressure. Symptoms of clonidine withdrawal include headache, nervousness, tremor, and hypertension. These three medications can be associated with significant withdrawal syndromes and require rescue strategies in the event the IT TDD system is interrupted. The rescue strategies for all three medications include oral medications but for higher doses of IT baclofen, intravenous baclofen may need to be given in the case of an abrupt cessation of the IT dosing.

Other conditions that mimic medication withdrawal should be excluded but if a pump and/or catheter malfunction is suspected the system should be evaluated. This can involve interrogating the pump, evaluation of the pump logs, programming bolus doses if necessary, imaging of the pump and catheter, reprogramming the pump and a complete assessment of the catheter (Fig. 26). In addition to aspirating the catheter through the catheter access port, the patient will need to have an evaluation of the pump's rotor and, depending on the clinical scenario, the pump reservoir itself may also need to be aspirated and the volume measured (Fig. 27).

5.1 Catheter and Rotor Study

In general, pump failures are unusual and medical conditions causing or mimicking withdrawal symptoms are more common (Farid 2017). Catheter failures are far more common than pump failures and despite recent improvements in the structure of the catheter these failures can include catheter kinking, twisting, and rupture (Varhabhatla and Zuo 2012).

The most common cause of pump failure is a motor stall, and this malfunction is readily detected when the pump is electronically interrogated. Most of the motor stalls occur spontaneously and have been found to occur at a rate of 2.4% when on-lable medications are used and at a rate of 7% with off-label medications when the stall rate is measured at 78 months post-implant (Riordan and Murphy 2015; Kosturakis and Gebhardt 2012; Diehn et al. 2011). Motor stalls also occur predictably and temporarily after MR imaging exams and pumps should always be interrogated after the exam to ensure resumption of normal function.

In addition to detecting motor difficulties with pump interrogation, motor stalls can be detected by fluoroscopy. The patient is placed under fluoroscopy to visualize the pump rotor (Fig. 27a). A spot radiograph or a last image hold is obtained to demonstrate and document the position of the pump rotor. A short and rapid bolus is then programmed into the pump so that will rotate the rotor a known amount. After that the radiograph can be repeated or the pump rotor may be visualized under live fluoroscopy to make sure it is still moving. Failure of the rotor to move the expected

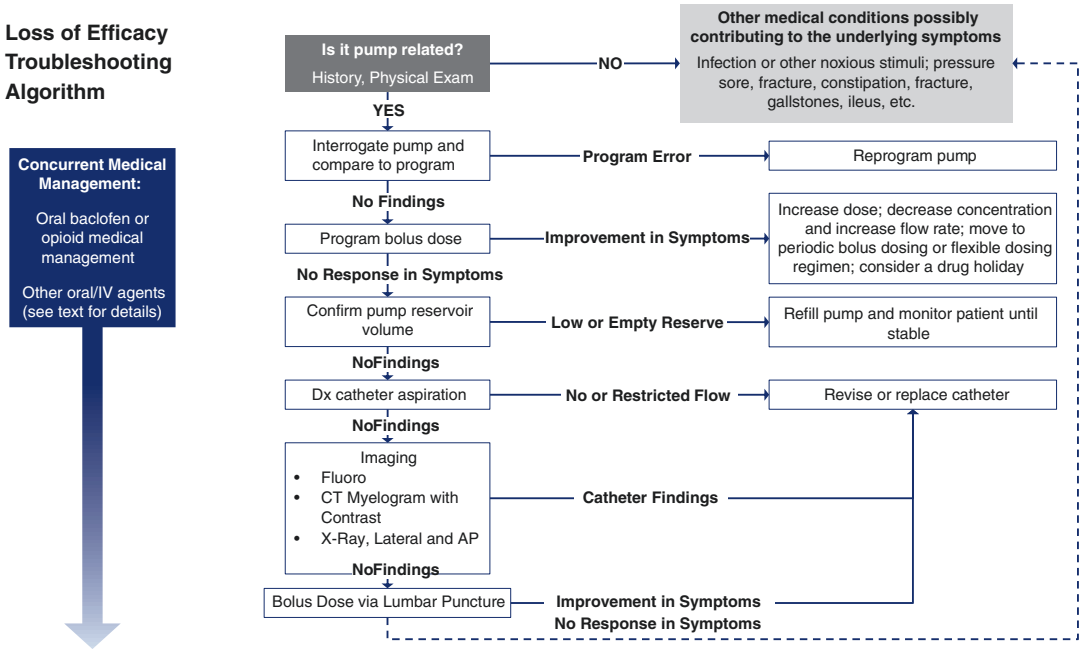

Fig. 26 Loss of intrathecal pump efficacy troubleshooting algorithm. *Dx* diagnostic, *AP* anterior-posterior, *CAP* catheter access port, *CT* computed Tomography, *ITB* intrathecal baclofen therapy, *LP* lumbar puncture. Adapted from: Farid R. Problem-Solving in Patients with Targeted Drug Delivery Systems. *Mo Med*. 2017;114(1):52–56

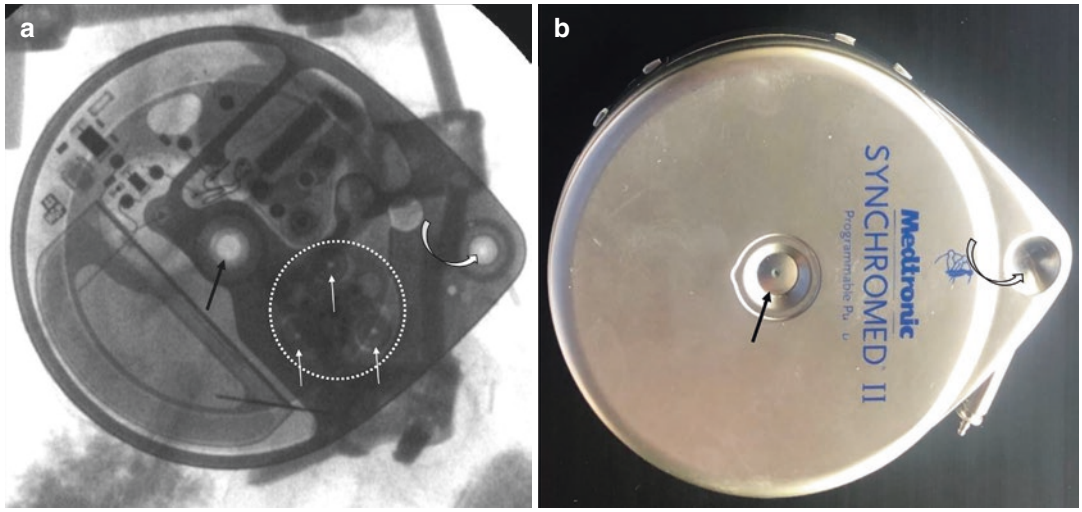

Fig. 27 (**a**, **b**) Fluoroscopic (**a**) and photographic views of the Medtronic SynchroMed II Intrathecal Pump demonstrates the rollers (white arrows in **a**) within the pump rotor (white dotted circle in **a**) as well as the pump refill port (black arrows in **a** and **b**) and the catheter access port (curved white arrows in **a** and **b**)

amount indicates a pump failure. In general, a rotor stall should not occur without an audible alarm, but the absence of hearing an alarm should not obviate the need for a rotor evaluation. If a rotor stall is detected, a prompt pump replacement may be necessary.

If the pump interrogation reveals no difficulties, the investigation should then turn to the

catheter. The catheter should then be aspirated via the catheter aspiration port (CAP) and 3–4 mL of fluid should be aspirated from the catheter. Free flowing clear fluid indicates a patent and appropriately functioning catheter but occlusion, bubbles, or poor return indicates an occluded or compromised catheter.

The catheter aspiration needle is a 25-gauge needle as opposed to the 22-gauge needle used for pump reservoir refills. This is a purposeful size discrepancy so the pump refill needle will not fit into the catheter aspirtion port (Fig. 27) resulting in an inadvertent injection of the entire contents of the pump refill medication into the patients CSF. The catheter aspiration is the most important diagnostic troubleshooting step because a much higher percentage of system malfunctions is attributable to catheter problems as compared to pump failure (Boster et al. 2014).

The catheter interrogation is accompanied by imaging studies such as X-ray, fluoroscopy, or computed tomography which will check for potential leakage, the catheter tip position and whether there is free flow of contract into the intrathecal space. Computed Tomography is the most useful of all of these modalities as this is the only modality that can accurately determine whether the catheter tip is located in a proper location intrathecally rather than located in an dural/epidural location (Fig. 28). The appropriate vertebral level can also be documented by X-ray, cone beam CT, or CT as the catheter tip is radiopaque (Fig. 17). Common catheter problems include disconnections from the pump or connector, kinking of the catheter, and repeated twisting of the catheter as a result of the pump becoming loose from the anterior abdominal wall and turning over within the pump pocket (Fig. 29). There are other techniques to identify catheter problems such as radioisotope studies using Indium 111 DTPA, but these examinations are used as commonly as they take much longer (≥2 days), are not nearly as anatomically specific as radiographic studies done with contrast and require

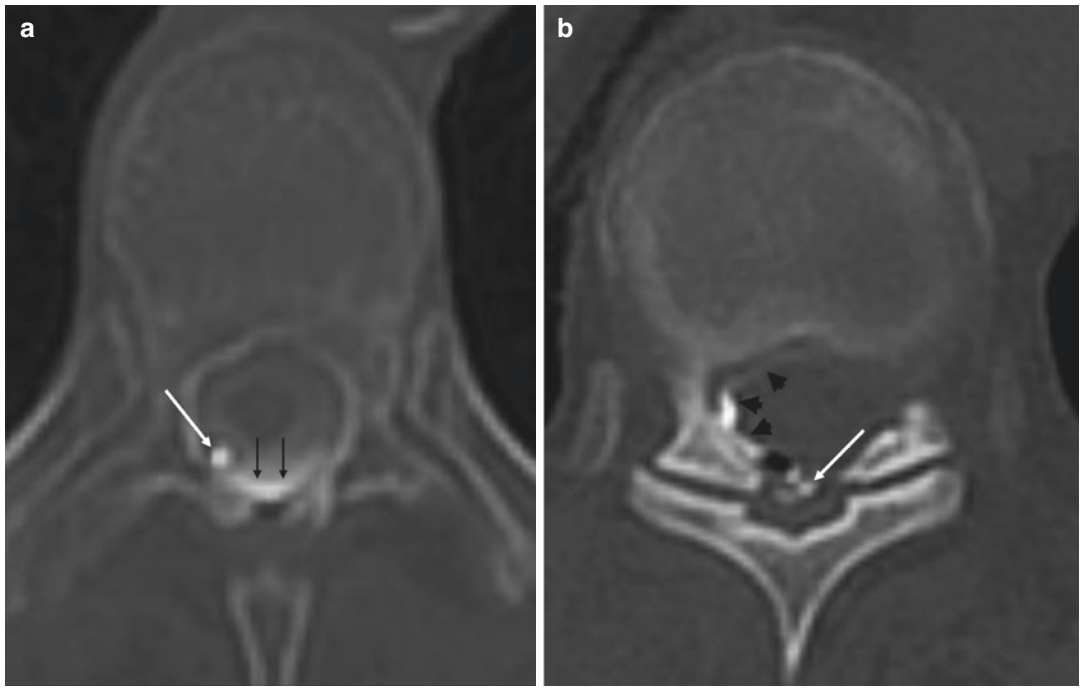

Fig. 28 (**a**, **b**) Axial CT images demonstrating the catheter (white arrows in **a** and **b**) and contrast layering in the intrathecal space (black arrows in **a**) in an appropriate position as compared to the contrast located outside of its expected position within the epidural space (white arrowheads in **b**)

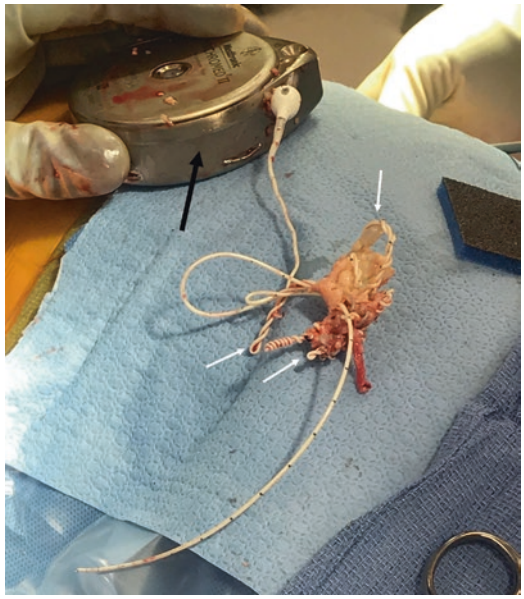

Fig. 29 A very twisted catheter (white arrows) connected to a 40 cm^3 SynchroMed II pump (black arrow) that was removed due to catheter blockage. The pump was found unattached to the abdominal wall within a loose and seroma filled pocket

precise flow rate calculations to predict the timing of the last imaging session (Boster et al. 2014).

When the catheter test is done, the catheter is first aspirated then once the medication in the catheter is cleared between 1 and 3 mL of contast is injected through the catheter, and the patient is scanned from superior to the catheter to through the inferior most aspect of the pump. The CT scan is analyzed to ensure appropriate pump position and integrity of the catheter as well as the appropriate contrast dissemination at the catheter tip (Fig. 28). If the catheter can't be aspirated, it is important to consider a number of factors before deciding whether it is safe. It is important to take into consideration the patients clinical status, what medication is in the pump and catheter, the prior exposure duration to the medication in the pump, the type of catheter, the length of the catheter lumen, and the amount of medication that may be injected into the CSF if the catheter proves to be patent. Based on that information, it may be necessary to prepare for a possible hospital admission for the patient to either be observed or supported (Dvorak et al. 2010; Miracle et al. 2011). All of these factors should be taken into consideration because a high pressure and volume injection of myelographic contrast can potentially unplug an obstruction and give the patient a medication overdose. It should also be known that given the ability of catheter injection studies to overcome small locations and other obstructions they can have a high false negative rate (Boster et al. 2014).

Over- or under-infusion of the pump medication is not common and is usually detected at the time of refill based on a discrepancy with the amount of medication that is supposed to be present in the pump reservoir and the amount that is actually aspirated. The treatment algorithm seen in Fig. 26 can be helpful in troubleshooting this situation especially if the patient is losing treatment efficacy. One of the most common causes of loss of efficacy and/or under-infusion is when the pump nears the end of its battery life. It is not unusual for a replacement pump to produce a greater medication treatment effect because of the new battery and slightly better pumping efficiency associated with the new system so after a pump replacement the medication dosage may need to be decreased. Monitoring the clinical response following pump or pump and catheter replacement is one of the reasons that overnight admission is recommended following replacement of the pump.

6 Conclusion

Intrathecal drug delivery has increased since its inception due to the work of clinicians, pharmacologists, and medical device manufacturers and has been facilitated by the recommendations of various consensus panels (Deer et al. 2004, 2007, 2010a, b, 2011, 2012a, b, 2017). There have been introduction of algorithms for the appropriate application of clinical therapies for patients with various types of pain and spasticity and encouragement for continued research and development for new medications, devices, and treatment recommendations. This chapter has provided an introduction for the appropriate use

of IT therapy in patients with neuropathic pain, nociceptive pain, and in patients with spasticity from various origins and has presented and explained the various components of IT drug delivery including the IT pump, the catheter, and the supplies for implanting the pump and catheter. We have also discussed the appropriate preoperative planning considerations and how to determine whether a patient is an appropriate candidate for IT therapy based on symptoms, overall health, prognosis, alternative treatments, and their response to the medication trial. Subjects like trialing of IT baclofen and various type of opioids are somewhat complex as is the management of ITB and IT pain patients so this has been discussed extensively and many treatment options and techniques have been introduced to successfully trial the medication and manage the patient once the pump has been implanted. The process of patient identification, pre-trialing management, IT trialing, preoperative patient management, surgical pump implantation, post-op management, and long-term medication management can be challenging without the appropriate knowledge and guidelines. In addition to the guidelines discussed above, the authors of this chapter have put forth their best helpful hints in the form of the Ten Commandments for the placement and management of intrathecal pumps (Tables 17 and 18, respectively). These can be combined with other consensus guidelines for determination of which patients would be candidates for IT therapy and which medication would be appropriate for a trial (Fig. 30). This chapter also goes into extensive detail on the surgical implantation of the IT pump including the optimal pump placement location, the appropriate patient positioning and identifies and explains some of the key steps in the pump implantation procedure. The major steps in the surgical implantation such as the pump pocket preparation, the catheter placement and tunneling, the connection of the pump and catheter, and the closure of the incisions are also covered

Table 17 Targeted drug delivery important tips—the ten commandments of intrathecal pump placement

1.	Use as large of a pump that the patient's preference and body habitus will allow
2.	Use peri-operative and wound antibiotics to reduce risk of infection
3.	Place the pump in the lower quadrant of the abdomen to facilitate patient comfort
4.	Do not place the pump at a depth that will make the refills overly challenging (don't place the pump too deep)
5.	Anchor the pump to the underlying fascia with durable permanent sutures
6.	In morbidly obese patients place the pump eight to nine cm lateral to the normal mid-clavicular line location. This will allows for a more superficial placement as the adipose tissue is typically less thick in this location
7.	Remember the blood patch as a treatment for a CSF leak around the catheter
8.	Always calculate the final implanted length of the catheter
9.	Always aspirate the catheter prior to closing the abdominal wound to ensure catheter patency
10.	Use an abdominal binder or the equivalent for 6 weeks following implantation

Table 18 Targeted drug delivery important tips—the ten commandments of intrathecal pump management

1.	Do not use systemic opioids (i.e. oral or transdermal) concurrently with IT opioids
2.	Do not use benzodiazepine medications in patients receiving IT opioid therapy
3.	Start with branded and single medications first then convert to compounded and multiple medications if necessary
4.	Make sure not to exceed the maximum concentrations of the compounded intrathecal medications
5.	Try to achieve the maximum time between refills to maximize patient comfort and convenience
6.	Use as large of a pump that the patient's preference and body habitus will allow
7.	If pump or catheter malfunction is suspected have a low threshold for conducting a catheter and rotor study
8.	Use the lowest amount of medication possible to accomplish the treatment goals
9.	Use the patient controlled intermittent bolus dosing feature when possible
10.	Reduction of systemic opioids prior to the trial or implantation improves the success of the IT therapy and allow s for better control of pain at a lower dose

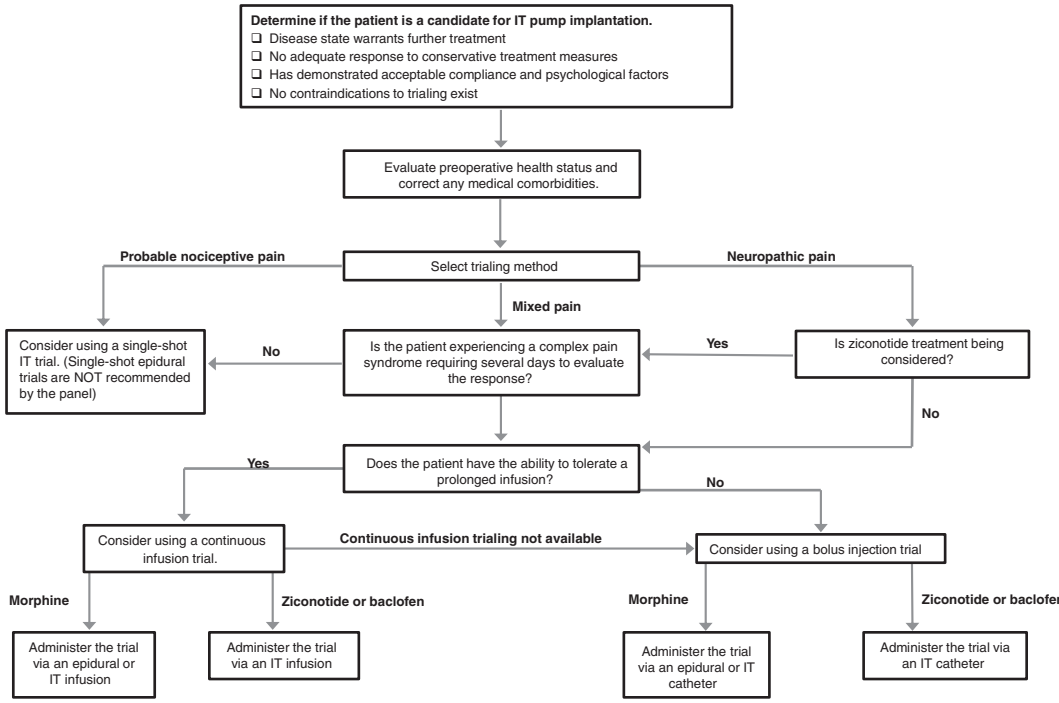

Fig. 30 Algorithm for trialing in patients who may be candidates for IT therapy for pain. Adapted from: Deer T.R., Prager J., Levy R., Burton A., Buchser E., Caraway D., Cousins M., De Andres J., Diwan 5., Erdek M., Grigsby E., Huntoon M., Jacobs M., Kirn P., Kumar K., Leong M., Liem L., McDowell G., Panchal SJ., Rauck R., Saulino M., Staats P., Stanton-Hicks M., Stearns L., Sitzman B.T., Wallace M., Willis K.D., Witt W., Yaksh T., Mekhail N. 2012. Polyanalgesic Consensus Conference-2012: Recommendations on Trialing for Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel. Neuromodulation 2012; 1S: 420–435

extensively and additional tips are provided to optimize the implantation and recovery and to make the system durable over time. In addition to the objective information provided and the extensive medical literature used in the preparation of this chapter, we have also provided subjective expert analysis and recommendations in order to help the reader enhance their practice as much as possible. Practitioners involved in any portion of the practice from patient identification to chronic IT patient management are encouraged provide their input in the form of registry involvement, clinical trial participation and manuscript production to foster and facilitate the production of high quality information associated with this therapy. The application of IT therapy is essential in certain patient groups, and there often is no substitute for this valuable therapy. These patients have been and continue to be under-recognized and under-treated and hopefully the information presented in this chapter can facilitate the appropriate identification, treatment, and patient management for those patients in need.

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