SNMMI procedure standard/EANM practice guideline for nuclear medicine evaluation and therapy of differentiated thyroid cancer

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ABSTRACT

The management of differentiated thyroid cancer (DTC) underwent a major paradigm shift in the past decade toward de-escalation of $^{131}$I therapy based on a risk-stratification approach. Radioiodine is used for the diagnostic imaging evaluation and therapy of DTC based on physiologic sodium-iodine symporter expression in normal and neoplastic thyroid tissue. We summarize the new concepts and essential information at the core of multidisciplinary DTC management, which emphasizes individualization of $^{131}$I therapy according to the patient’s risk for tumor recurrence in order to maximize benefit and minimize morbidity. The prognosis of DTC patients depends on the stage of disease at presentation and tumor biology plays an important role in long-term outcomes. In cases of radioiodine-refractory disease, additional management options include external-beam radiotherapy, interventional radiology for radiofrequency ablation, and systemic treatment using multikinase or tyrosine kinase inhibitors for achieving symptom relief and slowing disease progression. This document presents guidelines for $^{131}$I therapy decisions and $^{131}$I treatment response assessment in the context of staging, risk stratification and response evaluation criteria for DTC patients, as well as strategies for evaluation and management of non-iodine avid metastatic DTC.

Key words: Thyroid Cancer, Differentiated Thyroid Cancer, Standard of Care, Clinical Management, Clinical Guidelines, Procedure Standard.
ABBREVIATIONS

AJCC, American Joint Commission on Cancer; ATA, American Thyroid Association; CR, complete response; CT, computed tomography; DTC, differentiated thyroid cancer; Dx, diagnostic; EANM, European Association of Nuclear Medicine; ETA, European Thyroid Association; ETE, extrathyroidal extension; FDA, Federal Drug Administration; FDG, 18F-fluorodeoxyglucose; FNA, fine-needle aspiration; FTC, follicular thyroid cancer; HR, hazard ratio; LID, low iodine diet; MKI, multikinase inhibitors; MRI, magnetic resonance imaging; MTA, maximum tolerated 131I activity; MTV, metabolic tumor volume; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; NTCTCS, National Thyroid Cancer Therapy Cooperative Study Group; OS, overall survival; PFS, progression free survival; PET/CT, positron emission tomography/computed tomography; PFS, progression free survival; PT, post-therapy; PTC, papillary thyroid cancer; RR, relative risk; SNMMI, Society of Nuclear Medicine and Molecular Imaging; SPECT/CT, single photon computed emission tomography/computed tomography; SSR, somatostatin receptor; Tg, thyroglobulin; TgAb, anti-Tg antibodies; Tg-DT, Tg doubling time; Tg+/Scan-, elevated Tg and negative radioiodine scan; TIRADS, Thyroid Imaging Reporting and Data System; THW, thyroid hormone withdrawal; TSH, thyrotropin, thyroid stimulating hormone; rhTSH, recombinant human TSH; TLG, total lesion glycolysis; US, ultrasound; WBS, whole body scan; DxWBS, diagnostic WBS; PT-WBS, post-therapy WBS; WHO, World Health Organization.
PREAMBLE

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is an international scientific and professional organization founded in 1954 to promote the science, technology, and practical application of nuclear medicine. The European Association of Nuclear Medicine (EANM) is a professional non-profit medical association that facilitates communication worldwide between individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985. SNMMI and EANM members are physicians, technologists, and scientists specializing in the research and practice of nuclear medicine. The SNMMI and EANM will periodically define new guidelines for nuclear medicine practice to help advance the science of nuclear medicine and to improve the quality of service to patients throughout the world. Existing practice guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.

Each practice guideline, representing a policy statement by the SNMMI/EANM, has undergone a thorough consensus process in which it has been subjected to extensive review. The SNMMI and EANM recognize that the safe and effective use of diagnostic nuclear medicine imaging requires specific training, skills, and techniques, as described in each document. Reproduction or modification of the published practice guideline by those entities not providing these services is not authorized.

These guidelines are an educational tool designed to assist practitioners in providing appropriate care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, both the SNMMI and the EANM caution against the use of these guidelines in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the physician or medical physicist in light of all the circumstances presented. Thus, there is no implication that an approach differing from the guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of the guidelines.
The practice of medicine includes both the art and the science of the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these guidelines will not ensure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.
INTRODUCTION

DTC is a slow growing tumor with a very low disease-specific mortality rate for local-regional disease (5-year survival 99.9% for localized disease, and 98.3% for regional metastatic disease), however distant metastatic disease is associated with significantly worse prognosis (5-year survival 54.9%). (1) Standard of care management for differentiated thyroid cancer (DTC) includes risk-adapted surgery, post-operative Iodine-131 \(^{131}\text{I}\) therapy, and thyroid hormone therapy. In uncommon cases of radioiodine-refractory tumors, additional therapy may include re-operative surgical intervention, external radiotherapy and interventional radiology for treatment of locoregional metastases, and multikinase or tyrosine kinase inhibitors for treatment of distant metastatic disease.

EPIDEMIOLOGY AND CLASSIFICATION

Thyroid neoplasms are the most common endocrine tumors with annual incidence of 8-9 cases/100,000 people with substantial variability between and within populations. DTC accounts for more than 90% of cases, is more frequent in women, and has excellent specific mortality and prognosis in most cases. The rising incidence of thyroid cancer observed in the last 30 years is mainly due to the detection of small (≤ 2 cm) tumors as a result of increased imaging. (2) However, larger-size tumors (> 2 cm and > 5 cm size) have also increased in incidence; therefore, it is possible that there is a concomitant true rise in thyroid cancer incidence. (3) DTC is biologically and functionally heterogeneous with different molecular pathways impacting cancer cell biology, particularly BRAF V600E mutation is associated with reduced expression of all thyroid specific genes involved in iodine metabolism resulting in variable decreased responsiveness to \(^{131}\text{I}\) therapy. (4) The main clinical and pathological characteristics of DTC are summarized in Table 1. (5)

DIAGNOSIS

Neck ultrasound (US), serum thyroid stimulating hormone (TSH) and thyroid scintigraphy are used to select high-risk nodules for fine-needle aspiration (FNA) and filter out low-risk nodules from inappropriate additional procedures. Findings on US that are suspicious for thyroid cancer include hypoechogenity, solid consistency, microcalcifications, irregular margins, extrathyroidal extension (ETE)
and a taller than wide shape. (6) Sonomorphological nodule features have been used by several groups to produce a standardized risk assessment for thyroid malignancy named Thyroid Imaging Reporting and Data System (TIRADS). (7, 8) In the absence of suspicious cervical lymph nodes, FNA is discouraged for nodules less than 1 cm, and the decision to aspirate larger nodules is guided by the TIRADS score in the context of nodule size. Cytologic findings are classified according to risk of malignancy using the Bethesda System for Reporting Thyroid Cytopathology. (9) Certain cytologies are indeterminate, such as follicular neoplasm (or suspicious for follicular neoplasm) and the newly defined non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). In such cases, FNA can be complemented by the assessment of specific molecular alterations (e.g. BRAF or TERT mutations, RET fusions) as well as molecular imaging with $^{99m}$Tc-MIBI or $^{18}$F-fluorodeoxyglucose (FDG). (10)

THERAPY STRATEGIES

The current strategy for DTC management is a risk-stratified approach based on information from surgical histopathology, molecular markers, post-operative thyroglobulin (Tg) levels, and anatomic/functional imaging studies. (6)

Surgical treatment for DTC

Traditionally, (near-) total thyroidectomy was performed in most DTC patients, with lobectomy reserved for cytologically indeterminate nodules or patients with unifocal micro-PTC < 1 cm. The current American Thyroid Association (ATA) guidelines recommend lobectomy for patients with unifocal intrathyroidal low-risk DTC in the absence of additional risk factors (i.e. no clinical evidence of nodal metastases, cN0), although high level evidence is lacking. (6) The management of low-risk DTC between 2 and 4 cm is a topic of debate: While a lobectomy may be proposed, total thyroidectomy is still largely advised, especially in Europe. (11) Active surveillance has been recommended as an alternative to lobectomy for unifocal micro-PTC with no extracapsular extension or lymph node metastases. (12) The decision for active surveillance is based primarily on age-related risk of progression, individual surgical risk factors and patient preference. (13) In all other cases, total thyroidectomy remains the preferred surgical approach.
Cervical lymph nodal metastases occur in 20–60% of patients with DTC and this nodal involvement varies from clinically relevant macrometastasis to seemingly clinically irrelevant micrometastases. (14, 15) When lymph nodal metastases are diagnosed pre-operatively, central and/or lateral neck compartment dissection reduces the risk of local-regional recurrence. Prophylactic central neck dissection may improve regional control for invasive tumours (T3 - T4), but it is discouraged for low-risk DTC because potentially associated morbidities (i.e., hypoparathyroidism and recurrent laryngeal nerve damage) are not justified by a significant clinical benefit. (16) Preoperative neck US generally suffices to plan surgery; however, additional cross-sectional imaging (e.g., contrast enhanced computed tomography [CT], magnetic resonance imaging [MRI]) are used in locally advanced disease to inform the surgical approach. When iodinated contrast media are administered for preoperative CT, sufficient time (i.e., 4-6 weeks) for elimination of iodine load is required before performing radioiodine imaging and therapy.

Positron emission tomography/computed tomography (PET/CT) with $^{18}$F-FDG could be performed preoperatively in more aggressive DTC histotypes (i.e. poorly differentiated thyroid cancer or Hürthle cell carcinoma) and anaplastic thyroid cancer. (17) After surgery, the risk of structural disease recurrence and/or persistence is assessed using the three-tier (low, intermediate, high) stratification recommended by the American Thyroid Association (ATA) in 2009 and modified in 2015, (6) while the risk of mortality from thyroid cancer is estimated using the AJCC/TNM staging system. (18)

**Post-operative $^{131}$I therapy**

The goal of therapeutic $^{131}$I administration after total thyroidectomy is outlined based on standardized definitions as follows: remnant ablation, adjuvant treatment, or treatment of known disease. (19, 20) Upon integration of various parameters including clinical-pathologic, laboratory and imaging information, $^{131}$I therapy is administered for the following reasons:

- to eliminate normal thyroid tissue remnant in low-risk patients, thereby ensuring undetectable or minimal serum Tg levels (in the absence of neoplastic tissue), which facilitates follow-up (remnant ablation)
to irradiate suspected but unproven sites of neoplastic cells in low-intermediate and intermediate risk
patients as determined by histopathologic features, thereby reducing the risk of disease recurrence
\textit{(adjuvant treatment)}

- to treat persistent or recurrent disease in patients with demonstrated metastatic disease \textit{(treatment of
known disease)}

The impact of $^{131}$I therapy on the clinical outcome of thyroid cancer patients has been demonstrated in
several large dataseries. An analysis of 2,936 DTC patients in the National Thyroid Cancer Therapy
Cooperative Study Group (NTCTCS) reported improved overall survival and disease-specific survival in
patients with advanced tumors and regional and/or distant metastatic disease who received postoperative $^{131}$I
therapy. (21). An updated analysis of 4,941 patients in the NTCTCS study with a medium follow-up of 6
years (range 0 - 25 years) confirmed improved overall survival in stages III and IV patients, and also
demonstrated improved disease-free survival for stage II patients receiving $^{131}$I therapy. (22) A meta-analysis
of 31 patient-cohort studies regarding the effectiveness of $^{131}$I therapeutic administration demonstrated a
statistically significant effect on improving clinical outcomes at 10 years, with decreased risk for local-
regional recurrence (RR 0.31; CI 0.2 - 0.49) and an absolute risk reduction of 3% for distant metastatic
disease. (23) An analysis of the National Cancer Database comprising 21,870 intermediate-risk patients
demonstrated that adjuvant $^{131}$I treatment improved overall survival, both for the younger (< 45 years) and
for the older (≥ 65 years) subsets of patients. Adjuvant $^{131}$I therapy was associated with a 29% reduction in
the risk of death for all patients. (24) The beneficial effects of post-operative $^{131}$I therapy are most evident in
patients with local-regionally advanced and distant metastatic disease (stages IV-A, IV-B and IV-C disease):
an analysis of the National Cancer Database comprising 11,832 patients demonstrated that the
administration of $^{131}$I therapy was associated with significantly improved 5- and 10-year survival for both
PTC and FTC patients, regardless of pathological sub-stage (Stage IV A, B or C), as follows: mortality in the
PTC cohort (n=10,796) at 5 years at 10 years was 11% and 14% respectively in patients who received $^{131}$I
therapy, as compared to 22.7% and 25.5% respectively in patients who received none; mortality in the FTC
cohort (n=1,036) at 5 years at 10 years was 29.2% and 36.8% respectively in patients who received $^{131}$I
therapy, as compared to 45.5% and 51% respectively in patients who received none. (25) For patients with
distant metastases, a delay of greater than 6 months in administration of $^{131}$I therapy is associated with
decreased survival, demonstrated after a follow-up period of only 5-6 years. (26)

**Preparation for $^{131}$I therapy**

Evaluation with radioiodine scintigraphy and therapy is scheduled at a minimum of 4 weeks after
surgery, which allows time for patient preparation and for reaching post-operative Tg plateau levels, used as
a marker for residual thyroid tissue and/or metastatic thyroid cancer after total thyroidectomy. Tg is
synthesized exclusively in the thyroid follicular cells as a precursor of thyroid hormones and manipulation of
the thyroid gland during surgical resection releases significant Tg amounts in the systemic circulation. Tg is
subsequently metabolized in the liver with a mean elimination half-life (Tg t$_{1/2}$) of 65.2 hours. (27) Correct
timing of serum sampling for Tg measurement in regards to surgery is important, and measurements should
not be performed sooner than 25 days after total thyroidectomy to allow for clearance of the post-surgical Tg
peak (10 x Tg t$_{1/2}$). (27) Tg levels must always be interpreted in the context of concomitant TSH level
(unstimulated vs. stimulated Tg) and type of TSH stimulation (endogenous vs. exogenous). (28)
Thyroglobulin autoantibodies (TgAb) need to measured in conjunction with Tg in each serum sample
provided for Tg testing. Every specimen needs TgAb testing to authenticate that the Tg measurement is not
compromised by TgAb interference. When present, TgAb concentrations per se can be monitored as a
surrogate tumor marker. (29)

Patient preparation for optimal $^{131}$I uptake by residual thyroid tissue and metastatic disease includes
1-2 weeks of low iodine diet (LID) and adequate TSH stimulation (TSH ≥ 30 mIU/L measured 1 - 3 days
prior to $^{131}$I administration) by either thyroid hormone withdrawal (THW) or recombinant human TSH
(rhTSH) stimulation. (30) (31). However a recent paper showed that lower TSH levels may be sufficient for
remnant ablation without influencing remnant ablation success rates. (32) For childbearing females (age 12 -
50 year old) a negative pregnancy test is required to be obtained within 72 hours of $^{131}$I administration, or
prior the first rhTSH injection (if employed), unless the patient is status post hysterectomy or
postmenopausal.

Dietary deprivation of stable iodine ($^{127}$I) restricts consumption of iodine to < 50 mcg/day and is
important for minimizing interference with $^{131}$I uptake. In a study of 120 patients (LID group, n = 59, and
control group, n = 61) LID preparation decreased the 24-h urinary iodine excretion by 83% and increased
radioiodine uptake in thyroid remnants by 65% (p < 0.001) as compared to controls. The efficacy of $^{131}$I treatment (assessed at 6 months and defined by absent neck activity and Tg < 2 ng/mL and) was also improved by LID: successful ablation was achieved in 65% of LID patients as compared to 48% patients in the control group (p < 0.001). (33)

The dietary iodine consumption varies widely depending on ethnic culinary behavior, with reported average iodine intake of 195 mcg/day for Americans, 469 mcg/day for Koreans and 544 mcg/day for the Japanese. (34-36)

Patients’ compliance with LID can be confirmed by measurement of spot urinary iodine (USA reference range: 26–705 mcg/L) or urinary iodine/creatinine (I/Cr) ratio (USA reference range < 584 mcg/g Cr); World Health Organization (WHO) defines iodine status based on urinary iodine concentrations as follows: insufficient iodine intake <99 mcg/L; adequate iodine intake 100-199 mcg/L; iodine intake above requirements 200-299 mcg/L; excessive iodine intake ≥300 mcg/L (37).

In preparation for $^{131}$I therapy the state of iodine deprivation induced by LID is considered adequate when spot urinary iodine < 100 mcg/L, and optimal when urinary iodine < 50 mcg/L (or I/Cr ratio < 50 mcg/g Cr). (38) (39) A study of 101 patients comparing a 2-week vs. 4-week LID showed no significant difference in urinary iodine levels, both periods resulting in optimal I/Cr ratio for $^{131}$I therapeutic administration (i.e. < 50 mcg/g Cr). (40) Moreover, depending on the patients’ perceived difficulty with dietary iodine deprivation, their compliance with LID may decrease as the duration of LID is extended. Patients should be informed to avoid dietary supplements with high iodine content (e.g. iodine tablets [Iodoral]; spirulina tablets; red dye food colorants). In addition, the use of radiologic contrast agents and iodine-based antiseptics should be avoided for at least 4 - 6 weeks prior to $^{131}$I therapy administration. Medication review should always be performed, and in case of amiodarone usage, this medication should be replaced with a different anti-arrhythmic drug followed by serial serum/urinary iodine measurements over 3 – 6 months after amiodarone discontinuation to ascertain clearance of excessive iodine load before $^{131}$I treatment. Even if the urinary iodine levels did not reach the optimal values, the use of $^{131}$I therapy should be discussed in cases of advanced thyroid cancer.

See Table 2 for specific dietary information regarding LID preparation. (41)
TSH stimulation is used for increasing Na-I symporter (NIS) expression and function in metastatic lesions (and residual thyroid tissue) with the goal of increasing diagnostic sensitivity of $^{131}$I scintigraphy and radiation absorbed dose to target lesions. There are 2 major approaches for obtaining TSH stimulation:

**Endogenous TSH stimulation** is obtained through thyroid hormone deprivation following total thyroidectomy, thus inducing a hypothyroid state that must be carefully explained to patients in order to avoid major adverse consequences. For example, the patients must be informed regarding precautions about driving and/or restrictions for operating heavy machinery equipment since severe but reversible impairments in attention and reaction time can be observed. (42) The **hypothyroid stimulation protocol (THW)** has 2 variants, which are often employed in world-wide practice (although there is insufficient evidence in literature to prefer one variant over the other):

- **a) L-T4 (levothyroxine) withdrawal** for 4 weeks; this interval is determined by T4 elimination half-life (T4 t$_{1/2}$) of 7 days and the physiologic pituitary response to declining T4 concentrations. An acceptable variation involves repeated measurements of TSH during the second, third, and/or the fourth week of THW to expedite DxWBS and/or $^{131}$I therapy whenever possible, timing it to the TSH measurement of > 30 mU/L in case of metastatic disease (43). There is a level of unpredictability for scheduling the imaging and/or the therapeutic $^{131}$I administration with this latter approach. Lower TSH levels may be sufficient for thyroid remnant ablation in low-risk patients, according to a single study which did not find any influence of TSH levels on post-operative $^{131}$I remnant ablation success (defined as stimulated Tg < 1 ng/mL). The study involved 1873 patients without distant metastases, majority (~80%) stage I-II disease (of which 15% had TSH < 30 mU/L and demonstrated higher median Tg levels, suggestive of larger volume of thyroid remnant tissue). Since NIS activity (and consequently $^{131}$I uptake) are TSH-mediated in a dose-dependent and time-dependent manner, the area under the curve obtained by the TSH level plotted against time may achieve sufficient stimulation to result in the uptake of therapeutically effective $^{131}$I
activities for ablation of thyroid tissue remnants which have high constitutive NIS expression and function (32). However, the Guidelines Committee advises that this study findings cannot be extrapolated to high-risk patients and/or patients undergoing further $^{131}$I therapy for recurrent, persistent, or metastasized disease.

b) T4/T3 (levothyroxine/liothyronine) substitution for the first 2 weeks, followed by discontinuation of T3 for 2 weeks; this interval is based on T3 t1/2 of 0.75 days. In practice, T4 is stopped one day and T3 is started the next day in a typical dose of 25 mcg once or twice daily (depending on patient’s age and body weight). This regimen is well tolerated and has the advantage of minimizing hypothyroid symptoms. (44)

Occasionally, TSH level remains suboptimal for $^{131}$I therapy in patients with large thyroid remnants after surgery, in patients with limited pituitary functional reserve (e.g. history of head trauma, brain external beam radiation, pituitary surgery, obesity, other comorbidities), or in patients with functional metastatic disease. Correlation of laboratory results with the findings on post-operative diagnostic (Dx) radioiodine scintigraphy is helpful for determining the etiology of suboptimal TSH elevation. This helps guide further steps in management, such as surgical resection for large thyroid remnants or bulky residual cervical metastatic disease, or dosimetry-guided $^{131}$I therapy for secretory distant metastases. For patients with limited pituitary functional reserve, it is advisable to proceed with administration of exogenous TSH stimulation (rhTSH injections) to avoid further delay in $^{131}$I therapy administration and limit hypothyroid symptoms (rhTSH augmentation protocol).

**Exogenous TSH stimulation:** the patient continues T4 treatment and undergoes preparation with low-iodine diet. TSH elevation is obtained through administration of rhTSH (Thyrogen ® Stimulation Protocol): 0.9 mg rhTSH injection is administered intramuscularly on 2 consecutive days, followed by $^{131}$I therapy administration at 48-72 hours. (45) When diagnostic $^{131}$I scan is performed as an integral part of $^{131}$I therapeutic protocol (theragnostics), the tracer $^{131}$I activity is administered after the 2nd rhTSH injection and WBS scan is obtained 24 hours later, followed by subsequent $^{131}$I therapy administration.
The choice of preparation method (THW vs. rhTSH) needs to be individualized for each patient. The balance of the published data shows that for normal thyroid tissue (i.e. thyroid remnant ablation), rhTSH and THW stimulation are equivalent, because normal thyroid tissue has constitutive high expression of highly functional NIS and does not require prolonged TSH stimulation for adequate $^{131}$I uptake and retention. However, metastatic thyroid cancer has lesser density and poorer functionality of NIS, and therefore TSH elevation over time (area under the curve of TSH stimulation) is important to promote increased $^{131}$I uptake and retention in tumors. (46, 47). In the setting of metastatic disease, it is possible to use rhTSH stimulation on an off-label basis. However, the combination of THW preparation and dosimetry-guided $^{131}$I therapy are favored when clinically safe and the necessary expertise for dosimetry is available. (45, 48, 49) However, tumor vs. critical organ (e.g., bone marrow, lung) radiation absorbed dose (Gy) after rhTSH vs. THW-stimulation protocols need further evaluation. Furthermore, no studies have yet been performed comparing rhTSH and THW in patients with distant metastases regarding patient-relevant outcome measures (i.e., survival).

In contrast, the setting of adjuvant treatment is more complex regarding the use of rhTSH since this concept has only been introduced well after studies employing rhTSH for remnant ablation were completed. As a result, there is no clear data in literature allowing us to assess which of the two alternatives is better in the setting of adjuvant therapy separately from the setting of remnant ablation, especially with modern criteria for excellent response. However, rhTSH is registered for use for initial post-operative $^{131}$I therapy in patients up to and including N1 M0 disease. Therefore, in case of adjuvant treatment, rhTSH and THW should both be considered in accordance with the individual medical characteristics of the case, economic feasibility, quality of life and expected efficacy – in the latter part physicians’ experience may play a role in the absence of clear-cut studies. (20)

Post-operative thyroglobulin measurement

Although postoperative serum Tg measurement can provide valuable information with regard to the likelihood of achieving remission or having persistent or recurrent disease in response to an initial therapy, its predictive value (both negative and positive as regards residual disease) is significantly influenced by a wide variety of factors, as follows: the amount of residual thyroid cancer and/or thyroid remnants, the TSH
level at the time of Tg measurement, the functional sensitivity of the Tg assay, the time elapsed since total
thyroidectomy, the Tg cutoff used for analysis, and the individual risk of having radioiodine-avid loco-
regional or distant metastasis. (50) The fundamental role of Tg measurement in the monitoring of DTC
implies the need for high-quality Tg assays. A major problem that still hampers accurate Tg measurement is
the interference in the Tg assay by Tg antibodies (TgAb) and, more rarely, heterophile antibodies (HAb)
resulting in either an under- or overestimation of the serum Tg concentration. (51) Immunometric Tg assays
may also be subject to high-dose hook effect, leading to inappropriately normal or low serum Tg values in
sera with very high Tg concentrations, which require dilution for accurate measurement. (52) Absolute
threshold values for Tg, whether the patient is prepared with THW or rhTSH, remain controversial. Several
authors proposed that postoperative Tg values of about 10 ng/mL after THW, and of 1 ng/ml after rhTSH-
stimulation achieve the best balance of sensitivity and specificity for predicting recurrent or persistent
disease over time and poorer survival. (45, 53) Notably, as such results were obtained in patients treated with
131I following thyroidectomy, they cannot be translated to those patients treated by surgery alone and used to
decide for/against postsurgical 131I administration. Indeed, some studies not only excluded patients with anti-
Tg autoantibodies from analysis, but also excluded patients showing evidence of extra-cervical metastases,
introducing additional selection bias as regards translation of the data. Notably, iodine-avid tissue with a
responding undetectable stimulated serum Tg is detected in up to 20% of DTC patients by post-treatment
RAI whole body scan (WBS). Moreover, up to 6% of such patients had confirmed loco-regional or distant
metastases in addition to thyroid tissue remnants. (54, 55) In a retrospective study, Matrone et al. reported on
a group of 505 low- to intermediate-risk DTC patients who had undergone total thyroidectomy and rhTSH–
aided ablation with 1.1 GBq 131I. Just before ablation, a neck US was performed and Tg levels on thyroxine
were measured using a high sensitive assay (i.e. functional sensitivity of 0.1 ng/mL). A planar post-treatment
whole-body scan (PT-WBS) was performed and compared with pre-ablation basal Tg and US assessments.
Among the main findings, 150 patients had Tg levels less than 0.1 ng/mL and 1 of 150 showed cervical
persistence of disease; 287 patients had Tg levels between 0.1 and 1.0 ng/mL, 15 of whom had nodal or
distant metastases; and 68 patients had Tg levels exceeding 1.0 ng/mL, 11 of whom had neck metastases.
Notably, in the three patients with lung metastases, the basal Tg was 0.11 ng/mL, 0.12 ng/mL, and
0.94 ng/mL, respectively. A basal Tg level of 0.75 ng/mL was measured in one additional case of bone
This paper submits further evidence that basal Tg < 1 ng/mL cannot be used to rule out the presence of distant metastases; two of the four patients with distant metastases had Tg levels of 0.11 ng/mL and 0.12 ng/mL, respectively. (56)

Recently, Schlumberger et al. reported 5-year outcomes of ESTIMABL1, a randomised trial comparing four strategies of \(^{131}\)I administration following thyroidectomy in low-risk thyroid cancer. In this study, the rate of patients with persistent structural disease after \(^{131}\)I ablation was similar in the three subgroups of stimulated Tg ranges (i.e. \(<1 \text{ ng/mL}\), \(>1 \text{ to } \leq 5 \text{ ng/mL}\) and \(> 5 \text{ to } <10 \text{ ng/mL}\), respectively). (57, 58) In summary, with regard to decision-making on the need for postoperative \(^{131}\)I administration, it appears that the serum Tg value is more helpful in identifying patients for whom the administered \(^{131}\)I activity should be higher, rather than in identifying patients who do not require \(^{131}\)I therapy.

Radioiodine therapy planning

An important goal of \(^{131}\)I therapy is individualized treatment that maximizes benefit and reduces risk for each patient who is risk-stratified in the categories shown to be associated with improved outcomes after \(^{131}\)I therapy. There are two approaches to \(^{131}\)I therapy delivery: the approach integrating functional imaging information obtained with post-operative Dx radioiodine (\(^{123}\)I, \(^{131}\)I or \(^{124}\)I) scans in the management algorithm, (i.e. functional imaging-guided approach; theragnostics) and the approach based on clinical-pathologic factors and institutional protocols (i.e. risk-adapted approach). Which approach is chosen depends on local factors, including the quality of surgery, the availability of, and expertise with various imaging modalities, and physician as well as patient preferences. Each approach has strengths and limitations, and no conclusive evidence is available with regard to primary outcome measures to allow recommending one strategy over the other.

Management integrating functional diagnostic radioiodine imaging

This theragnostic approach to \(^{131}\)I administration involves the acquisition of a postoperative Dx radioiodine (\(^{123}\)I, \(^{131}\)I or \(^{124}\)I) scan for planning \(^{131}\)I therapy. Dx whole body scans (WBS) are performed with the intent of identifying and localizing regional and distant metastatic disease, as well as evaluating the capacity of metastatic deposits to concentrate \(^{131}\)I. Depending on institutional protocols, the findings on
Dx WBS may alter management, such as providing guidance for additional surgery or altering the prescribed 
$^{131}$I therapy, either by adjusting empiric $^{131}$I activity, or by performing dosimetry calculations for determining 
the maximum tolerated therapeutic $^{131}$I activity (MTA) for treatment of distant metastatic disease. Also, 
unnecessary $^{131}$I therapy may be avoided if Dx WBS finds no evidence of residual thyroid tissue or 
metastatic disease and the stimulated Tg is <1 ng/mL in the absence of interfering TgAb. Information 
acquired from DxWBS may also lead to additional functional metabolic imaging with $^{18}$F-FDG PET/CT 
when non-iodine avid metastatic disease is suspected (based on Tg elevation out of proportion to the findings 
on DxWBS). Wherever available, it is preferable for postoperative Dx scanning to be performed using 
integrated multimodality imaging (i.e., single photon computed emission tomography/computed tomography 
(SPECT/CT).

DxWBS with or without SPECT/CT may detect metastases in normal-size cervical lymph nodes (that would 
not be visible on post-operative neck ultrasonography), may identify pulmonary micro-metastases (which are 
too small to be detected on routine chest x-ray and may remain undetected on computed tomography) and 
may diagnose bone metastases at an early stage before cortical disruption is visible on bone x-rays or CT. 
Most importantly, since $^{131}$I therapy is most effective for smaller metastatic deposits, early identification of 
regional and distant metastases is important for successful therapy.(60) (61)

Clinical experience with diagnostic $^{123}$I scans demonstrated their usefulness in thyroid cancer 
management: pre-ablation $^{123}$I WBS provided additional critical information in 25% of 122 patients, by 
revealing unsuspected regional or distant metastases and thus guiding the administration of higher $^{131}$I 
therapeutic activities, or revealing unexpected large thyroid remnants (62). In a cohort of 152 consecutive 
patients referred for post-operative $^{131}$I ablative therapy, the information provided by Dx $^{123}$I WBS led to a 
change in prescribed therapeutic $^{131}$I activity in 49% of cases compared to the recommended $^{131}$I activities 
based on surgical pathology alone. (63) In a study based on the review of 355 Dx radioiodine scans (after 
administration of 37 – 148 MBq [1- 4 mCi] of either $^{123}$I or $^{131}$I) the imaging findings altered the patients’ 
management plan in 29% of cases.(64) Similar conclusions have been reached by other investigators as well 
who demonstrated that the information obtained from Dx $^{131}$I WBS changed the prescribed therapeutic $^{131}$I 
activity in 58% cases (65).
A study comparing the diagnostic sensitivity for disease detection for Dx. 74-185 MBq (2–5 mCi) 

$^{123}$I WBS versus 111–185 MBq (3–5 mCi) $^{131}$I WBS (both performed after THW protocol) demonstrated that, although $^{123}$I is adequate for imaging residual thyroid tissue, it appears to be less sensitive than $^{131}$I for imaging thyroid cancer metastases: $^{123}$I missed metastases shown by $^{131}$I in the neck, mediastinum, lungs, and bone. No lesion was better seen with $^{123}$I than with $^{131}$I. Other authors also found Dx $^{123}$I WBS to be insensitive for metastatic disease detection, and attributed this finding to the short half-life of $^{123}$I (13 h), limiting imaging to no later than 24 hours post-injection, which is too short for optimizing tracer tumor uptake. Other authors also found Dx $^{123}$I WBS to be 

In addition to the radioiodine isotope used, the preparation protocol (THW vs. rhTSH stimulation) has also an impact on the diagnostic sensitivity of DxWBS for disease detection: across two phase-3 clinical trials enrolling 358 patients, the rhTSH-stimulated DxWBS failed to detect remnant and/or cancer localized to the thyroid bed in 16% of patients in whom it was detected by a DxWBS obtained after thyroid hormone withdrawal. In addition, the rhTSH-stimulated DxWBS failed to detect metastatic disease in 24% of patients in whom it was detected by a THW DxWBS. In a group of 320 thyroid cancer patients referred for postoperative $^{131}$I therapy, Dx $^{131}$I WBS with SPECT/CT imaging obtained after THW protocol detected regional metastases in 35% of patients, and distant metastases in 8% of patients. This information changed staging in 4% of younger, and 25% of older patients. Both imaging data and stimulated thyroglobulin levels acquired at the time of Dx $^{131}$I WBS were consequential for $^{131}$I therapy planning, providing information that changed clinical management in 29% of patients compared to a management strategy based on clinical and surgical pathology information alone. 

The benefits of integrating Dx $^{131}$I WBS in the management algorithm of intermediate- and high-risk thyroid cancer for guiding $^{131}$I therapeutic administration have been demonstrated in a group of 350 patients who were evaluated to assess therapy response with a median follow-up of 3 years after primary treatment strategy (surgery and postoperative $^{131}$I therapy): complete response (CR) to therapy was achieved in 88% patients with local-regional disease, and in 42% patients with distant metastases after a single $^{131}$I therapeutic administration. Further studies for evaluating long term outcomes of these patients need to be performed.
Depending on the type of patient preparation, Dx. radioiodine ($^{123}$I or $^{131}$I) activities such as 37 – 74 MBq (1-2 mCi) for THW protocols and 110-148 MBq (3-4 mCi) for rhTSH-stimulation protocols are frequently used. (39) The higher tracer activity (3-4 mCi) employed for the rhTSH-stimulation protocols is to compensate for the competitive inhibition exerted by the iodine content of L-T4 (levothyroxine) on the uptake of radioiodine ($^{131}$I or $^{123}$I) in thyroid tissue or metastatic lesions. (74) L-T4 contains 63.5% iodine by molecular weight. The interference of L-T4 stable iodine content on radioidine uptake is not surprising if we consider that the amount of iodine in 1.1 GBq (30 mCi) is only 5 µg, as compared to 50 µg stable iodine content in a daily dose of L-T4. (75) The dilution of radioidine with nonradioactive iodine from any source may degrade WBS image quality and reduce the effectiveness of $^{131}$I therapy. Replacement of levothyroxine with liothyronine (L-T3) during the preparation period for rhTSH-stimulation protocols has been proposed for decreasing the dilution effect of nonradioactive iodine on the uptake of radioidine. (74) L-T3 has a lower iodine content of 56.6% and it is estimated to exert an equivalent effect with ¼ of L-T4 dose. (76) In addition to a low iodine diet, this therapeutic interchange from L-T4 to L-T3 during the preparatory period for rhTSH stimulation protocol resulted in a further decrease in 24-h urinary iodine excretion by 56%, as compared to L-T4 treatment. (74)

Optimization of imaging acquisition parameters and current SPECT/CT gamma camera technology permit good quality visualization of distant metastatic disease using 37 MBq (1 mCi) $^{131}$I Dx. activity. (71, 72, 77, 78).

In all cases, $^{131}$I therapy administration should be followed by a post-therapy whole-body scan (PT-WBS) to determine therapeutic $^{131}$I localization which is routinely used to complete post-operative staging.

However, the day to perform the PT-WBS after therapeutic $^{131}$I administration remains controversial, ranging from 2–10 days. (79) PT-WBS acquisition on two separate days may be valuable as demonstrated by Salvatori et al. in a group of 134 patients who underwent both early (at 3 days) and delayed (at 7 days) scans: 80.5% of detected lesions were concordant on both early and delayed scans; however, 7.5% lesions were detected only on the early scans, while 12% lesions were detected only on the delayed scans. (80) By performing both early (at 3 – 6 days) and delayed (at 10 – 11 days) PT-WBS, Hung et al. reported that 28% of nodal metastases, 17% of lung metastases and 16% of bone metastases were visible only on the early scans. (81) This is consistent with the observation that $^{131}$I therapeutic activities produce destructive cellular
effects with resultant increased rate of $^{131}$I loss from the tissue; this accelerated tissue $^{131}$I loss after treatment accounts for the discrepancies reported between DxWBS and delayed PT-WBS in earlier studies and interpreted as “stunning”, as well as the differences observed between the early and delayed PT-WBS. (82) However, delayed PT-WBS acquisition provides the advantage of increased contrast resolution due to time-dependent $^{131}$I clearance from normal tissues: Chong et al. reported in a group of 52 patients that 22% of lung metastases and 33% of bone metastases were visible only on the delayed PT-WBS (obtained at 7 days). (83) Similarly, Kodani et al. reported in a group of 24 patients that 29% of lung metastases and 20% of bone metastases were visible only on the delayed PT-WBS (obtained at 7-9 days). (84)

Hybrid imaging with SPECT/CT improves the accuracy of PT-WBS and should be done whenever possible. A systematic review of 14 original research articles describing the incremental value of $^{131}$I SPECT/CT demonstrated significant clinical benefit in terms of staging, risk stratification, alteration of management and/or follow-up of DTC. (85) This is especially important when DxWBS was not performed, or when PT-WBS shows additional foci of activity as compared to DxWBS. (86) A high level of concordance between DxWBS and PT-WBS findings has been demonstrated in 2 large single-institution data series from Stanford University (98% concordance in a group of 280 patients) and University of Michigan (92% concordance in a group of 303 patients). (87) (71). In summary, DxWBS can be very valuable 1)for $^{131}$I therapy planning in the paradigm of thyroid cancer theragnostics. (88)

Dx. WBS scintigraphy performed in follow-up evaluation after initial post-operative $^{131}$I administration is important to 1) establish a new baseline after postoperative $^{131}$I therapy, (89) 2) determine interval response to $^{131}$I treatment, and 3) assess the patient’s thyroid cancer status. Along with basal and stimulated Tg testing and cross-sectional anatomic imaging, the results of follow-up Dx WBS contribute to dynamic risk restratification, which is usually performed at 6 – 12 months after initial treatment strategy (surgery and postoperative $^{131}$I therapy). For patients with rising Tg levels, Dx WBS and PET/CT evaluation can be scheduled sequentially to asses for recurrent and/or metastatic disease and evaluate tumor biologic behavior for determining if the patient would benefit from additional $^{131}$I therapy. (73) Importantly, a recent report examining the results of a large SEER database (28,220 patients diagnosed with DTC between 1998 and 2011) showed that follow-up Dx WBS performed after primary treatment of DTC are the only imaging
studies associated with improved disease-specific survival, demonstrating the clinical benefit of $^{131}$I theragnostics for DTC management (90).

Sample protocols for the integration of Dx. WBS evaluation, $^{131}$I therapy delivery and PT-WBS imaging after THW and after rhTSH stimulation are provided in Figure 1 and Figure 2, respectively. Figure 3 and Figure 4 present sample protocols for dosimetry-guided radioiodine theragnostics after THW and after rhTSH stimulation, respectively.

Risk-based management followed by post-therapy $^{131}$I scans with diagnostic intent

The risk-based approach is generally used for thyroid remnant ablation and for adjuvant $^{131}$I treatment. Empiric activity selection is the most commonly used approach in advanced DTC, in which the nuclear medicine physician chooses an activity based on convention, availability, experience with various imaging modalities and patient-related parameters. With this therapeutic approach patients are most commonly given activities of 1.1 GBq (30 mCi), 1.85 GBq (50 mCi), 3.7 GBq (100 mCi), 5.6 GBq (150 mCi), or 7.4 GBq (200 mCi). (91) Although there are theoretical disadvantages of this approach, compared to dosimetric strategy in the treatment of loco-regional and metastatic disease, no recommendation can be made for the superiority of one method of $^{131}$I application over another. However, it is essential to emphasize that maximum tolerated activity (MTA) can be exceeded in patients undergoing empiric $^{131}$I therapy escalation for treatment of advanced DTC, which may cause acute dose-related toxicities. Likewise, patients may be undertreated with this conventional therapeutic approach. (92) Kulkarni et al. studied the frequency of overtreatment and undertreatment for various empiric $^{131}$I activities in patients with metastatic DTC. They performed 127 dosimetric studies based on MTA of $^{131}$I that would deliver a radiation dose of 2 Gy to the blood. In case of empiric activities of 3.7 GBq (100 mCi), 5.6 GBq (150 mCi), 7.4 GBq (200 mCi), 9.25 GBq (250 mCi), and 11.1 Gbq (300 mCi) of $^{131}$I, the percentage of treatments in which patients would theoretically exceed the MTA according to dosimetry calculations, was < 1%, 5%, 11%, 17%, and 22 %, respectively. (93) Tuttle et al. retrospectively analyzed 535 dosimetric studies performed in 328 thyroid cancer patients with normal renal function. The dosimetry was based on the MTA that would deliver a radiation dose of 2 Gy (200 rads) to the blood or 2.96 GBq (80 mCi) retained at 48 h if there were diffuse lung metastases. They found that empirically applied $^{131}$I activity of 7.4 GBq (200 mCi) theoretically exceeds...
MTA in 8%–15% of patients younger, and 22%–38% of those older than 70 years. Administration of 9.25
GBq (250 mCi) of $^{131}$I may exceed MTA in 22% of patients younger, and 50% of patients older than 70
years. Additionally, radioiodine-avid diffuse bilateral lung metastases were associated with a lowering of
MTA to less than 9.25 GBq (250 mCi). (94) In conclusion, caution should be exercised in applying an
empiric approach with activities greater than 5.6 GBq (150 mCi), especially in the elderly, in patients with
radioiodine-avid diffuse bilateral pulmonary metastases, and renal insufficiency. (93)

However, there are no prospective randomized controlled comparative studies that would address the
optimal therapeutic approach with the best treatment response and patients’ outcome. Klubo-Gwiedzinska
et al. retrospectively compared the treatment efficacy and side effects of empiric and dosimetry-based
prescribed activities of $^{131}$I in patients with locoregionally advanced or metastatic disease. The latter
approach was based on a calculation of MTA of $^{131}$I that would deliver a radiation dose of 2 Gy (200 rads) to
the blood. They enrolled 87 patients followed for 51 ± 35 months, of whom 43 were treated with dosimetry-based
and 44 with the empiric-based approach. Patients treated with the dosimetry-based strategy were 71%
less likely to progress (odds ratio 0.29) and more likely to achieve complete response compared to those
treated with empiric activities (odds ratio 8.2). In the dosimetry-based group, there was a positive correlation
between the complete response and percentage of MTA given as the first treatment of $^{131}$I. Complete
response was especially pronounced in patients with the locoregional disease treated according to dosimetric
strategy (35.7% vs. 3.3% in empiric strategy group). There was no significant difference in the frequency of
side effects between the two groups. (95) Deandreis et al. retrospectively analyzed 352 patients with
radioiodine-avid metastatic DTC treated with $^{131}$I by an empiric fixed activity of 3.7 GBq (100mCi) or
whole-body/blood clearance dosimetry with activities 2.7-18.6 GBq (73-503 mCi), during the median
follow-up of 7.2 years. The five-year OS in patients treated with empiric and dosimetric strategies were 96%
and 96% in patients younger than 40 years with micrometastatic disease, 70% and 65% in the group of
patients older than 40 y with macrometastases or multiple metastases, and 92% and 87% in younger patients
with macrometastases or older patients with micrometastases, respectively. Thus, there was no statistical
difference in five-year OS between the two groups. (96) However, as noted by Flux et al. there were no
correlations with the whole-body (blood) absorbed doses or the administered activity, important factors to
generate adequate outcomes. (97) There is increasing evidence for a correlation between the radiation
absorbed doses delivered and the patients’ outcomes. (98) Each retrospective study is characterized by a risk of selection bias. When retrospectively comparing the two treatment regimens, we should take into account that patients are assigned to a particular treatment mainly based on the severity of the disease.

The administration of empiric $^{131}$I activities of $\leq 3.7$ GBq ($\leq 100$ mCi) is generally not recommended for the treatment of locoregionally advanced and/or distant metastatic DTC, as these patients require escalation of $^{131}$I therapeutic activity and an individualized treatment approach. Particularly in the setting of diffuse iodine-avid distant metastatic disease the attending physician or managing medical team should consider either performing dosimetry or referring the patient to a site which performs dosimetry-guided $^{131}$I therapy for two reasons: 1) to identify those patients who would have a higher likelihood of side effects if $\geq 5.6 - 7.4$ GBq (150 - 200 mCi) $^{131}$I therapeutic activity is administered, and/or 2) to administer the highest safe $^{131}$I therapeutic activity (MTA) for maximizing tumor radiation absorbed dose.

For addressing the current controversy regarding when to use conventional (empiric) vs. dosimetry-guided $^{131}$I therapy, there is a need for prospective, randomized, controlled, comparative studies for determining the superiority of one method of $^{131}$I application over another in specific clinical settings. (99) This should be done in combination with lesion dosimetry to estimate the lesion absorbed dose. The current evidence, although potentially biased, suggests that dosimetry-based high-activity $^{131}$I therapy in patients with advanced DTC may be more effective in improving patients’ outcomes and survival.(100, 101)

Each $^{131}$I therapy should be followed by post-therapeutic $^{131}$I imaging (PT-WBS). There are distinct advantages offered by post-surgery $^{131}$I activity administration for all risk stratification categories and irrespective of post-operative thyroglobulin levels, confirming the role of PT-WBS for early detection and treatment of local-regional and distant metastatic disease. Park et al. demonstrated in a large cohort of 824 DTC patients who underwent $^{131}$I therapy after L-T4 withdrawal protocol that 52 patients (6.3%) had functioning metastases identified on post-Rx scans despite stimulated Tg $\leq 2$ ng/ml in the absence of interfering anti-Tg antibodies (Tg-Ab). A low stimulated Tg $\leq 2$ ng/ml did not exclude the presence of distant metastases, since in this group 7 patients (13.5%) had pulmonary and osseous metastases while the remainder 45 patients (86.5%) had cervical/mediastinal lymph nodal metastases. (55) In a recent study by Campenni et al. in 570 low- and low-intermediate risk DTC patients (pT1 - pT3) post-Rx scans with
SPECT/CT demonstrated metastases in 82 patients (14.4%), of which 73 patients (90.2%) had post-surgical nonstimulated Tg ≤ 1 ng/ml; furthermore, in 44 patients (54%) stimulated Tg remained ≤ 1 ng/ml, despite the presence of metastases on post-Rx scans. (102) Therefore, post-surgical nonstimulated Tg levels cannot be used independently in deciding whether to pursue therapeutic $^{131}$I administration, mainly in the patients assigned as low-risk category based solely on surgical pathology information. The body of published evidence regarding the outcome of postoperative $^{131}$I ablation in low-risk patients (which in current terminology would encompass both remnant ablation and adjuvant treatment) demonstrates that these patients can be fully reassured by a complete treatment response and would not require Tg stimulation testing or periodic neck US examinations during long-term follow-up. (103) In fact, cohorts in which all patients, - including low-risk ones with non-metastasized, non-microcarcinoma disease, - received $^{131}$I therapy after surgery, demonstrated that life expectancy is normal for > 85% of patients – only patients with stage IV disease at diagnosis have a reduction of life expectancy. (104, 105) We are not aware of similar data available for individualized or more restrictive $^{131}$I prescription strategies.

In conclusion, as detailed above, post-operative Tg levels are helpful in identifying high-risk patients that require higher $^{131}$I activity, but cannot be used for ruling-out $^{131}$I therapy. Omission of the procedure exposes the patients to the risk of late diagnosis of residual disease. (106, 107) Finally, early reassurance and more reliable follow-up are only possible when patients had received total thyroidectomy followed by postoperative $^{131}$I therapy.

**Determining the prescribed therapeutic $^{131}$I activity**

Current practice guidelines recommend routine $^{131}$I adjuvant therapy for patients with intermediate to high risk of recurrence (although there are some differences concerning intermediate risk disease) and avoiding routine $^{131}$I therapy for patients with a small ($\leq$1 cm) intrathyroidal DTC and no evidence of locoregional or distant metastatic spread. (6, 91) However, $^{131}$I therapy for other low-risk DTC patients (i.e. pT1b - T2) remains controversial: the various iterations of the ATA guidelines advised against the systematic use of $^{131}$I in these patients,(6) while the 2008 European Association of Nuclear Medicine (EANM) suggests that $^{131}$I therapy is helpful, citing the lack of prospective data showing that surveillance without ablation is non-inferior to $^{131}$I administration. (108) Indeed, the ATA, the EANM, the SNMMI and the European
Thyroid Association (ETA) recently published a joint statement acknowledging the absence of high-quality evidence either for or against the post-operative use of $^{131}$I in low-risk patients. (20)

The decision for $^{131}$I therapy and the prescribed $^{131}$I activity depends on the goal of $^{131}$I therapy as determined by the estimated risk for persistent/recurrent disease. Please see Table 3 for suggested treatment $^{131}$I activities in the context of therapeutic intent, as follows:

- **Thyroid remnant ablation** in low-risk patients is typically performed with low $^{131}$I activity (e.g., 1.1 - 1.85 GBq [30 mCi - 50 mCi]) based on the preponderance of published evidence demonstrating equal effectiveness as compared with higher $^{131}$I activities, with lower rate of adverse events. (109-145) The Federal Drug Administration (FDA) approved the use of rhTSH (Thyrogen®, Genzyme corporation) in combination with 3.7 GBq (100 mCi) $^{131}$I for remnant ablation in December 2007. (68, 146, 147)

- **Adjuvant $^{131}$I therapy** is performed with 1.85 - 3.7 GBq (50 - 100 mCi), with some institutions extending this range to 5.6 GBq (150 mCi); there are no comparison data regarding the effectiveness of 3.7 GBq (100 mCi) vs. 5.6 GBq (150 mCi) for adjuvant treatment, while current guidelines advise that the risk for $^{131}$I toxicity increases with therapeutic activity escalation. (148)

- **Treatment of known disease** is performed with 3.7 - 5.6 GBq (100 – 150 mCi) for small volume local-regional disease, and 5.6-7.4 GBq (150-200 mCi) $^{131}$I for treatment of advanced local-regional disease and/or small volume distant metastatic disease. Identification of iodine-avid diffuse metastatic disease may lead to escalation of prescribed therapeutic $^{131}$I activity to $\geq$ 7.4 GBq (200 mCi) guided by dosimetry calculations. (73, 149, 150).

A special circumstance is presented by use of $^{131}$I therapy (3.7 GBq [100 mCi]) for ablation of a remaining thyroid lobe after lobectomy/hemithyroidectomy as an alternative to completion thyroidectomy. (151-153). Current guidelines propose lobectomy for patients deemed as low-risk for recurrence; however, if the pathology demonstrates a higher risk tumor, then completion thyroidectomy with resection of the contralateral thyroid lobe is recommended with the goal of facilitating post-operative $^{131}$I therapy and long-term surveillance. Therapeutic $^{131}$I administration as a substitute for completion thyroidectomy is not recommended routinely. (6) However, it can be used to eliminate the residual thyroid lobe in highly selected cases, such as patients who had experienced complications during initial surgery (e.g. recurrent laryngeal nerve paralysis), for whom completion thyroidectomy is contraindicated due to other comorbidities, or for
patients who decline additional surgery. There are limited data regarding the long-term outcomes of this approach. The data suggest similar clinical outcomes with a slightly higher proportion of patients with persistently detectable Tg. In a randomized controlled equivalence trial of 136 low-risk DTC patients treated with lobectomy, which compared low- vs. high $^{131}\text{I}$ activities in achieving successful ablation of the remaining lobe, the remnant ablation success rate was significantly higher (75% success rate) using 3.7 GBq [100 mCi], as compared with 1.1 GBq [30 mCi] (54% ablation success rate); mild to moderate short-term neck pain was more frequently reported in the high-activity group (66%) compared with the low-activity group (51%). Prednisone treatment for neck pain was used more frequently in the high-activity group (36% of patients) than in the low-activity group. (154)

**Dosimetry-guided $^{131}\text{I}$ Therapy**

There are two approaches for individualization of $^{131}\text{I}$ therapy based on dosimetry calculations, as follows: (1) blood or bone-marrow dosimetry-based methods, primarily targeting safety, and (2) lesion dosimetry-based methods, primarily targeting efficacy. Of these, the classic blood-based method is more widely used, and permits calculation of the maximum tolerated activity (MTA) that can be administered to an individual patient without the risk of severe hematopoietic toxicity. In this dosimetry-based regimen, the radiation absorbed dose to the blood is used as a surrogate for the absorbed dose to the red bone marrow, typically considered as the dose limiting critical organ in the majority of cases. An upper limit of 2 Gy to the blood is generally used as the threshold that minimizes serious bone marrow toxicity and pulmonary $^{131}\text{I}$ retention should not exceed 3 GBq (80 mCi) after 48h, which is based on the findings of the original study of Benua et al. (155) Therapy individualization is based on determining the maximum $^{131}\text{I}$ activity that can be administered to each patient while keeping the absorbed dose to the blood at $\leq 2$ Gy and not exceeding pulmonary retention limits. Blood based dosimetry is carried out by measuring activity counts in blood samples obtained at specified time points after the administration of a tracer amount of $^{131}\text{I}$, as described in a standardized operating procedure by the EANM Dosimetry Committee. (156) The contribution to the absorbed dose from beta radiation originating from the activity in the blood, as well as the contribution from gamma-ray emissions originating from the activity throughout the whole-body must be considered, although the latter component is usually $< 25\%$. To determine the blood activity, whole blood samples (5 ml
heparinized aliquots) are collected at multiple time points (2, 24, 48, 72 and 96 hours) during the first week after administration of tracer amount (e.g. 15 - 74 MBq [0.4 - 2 mCi]) $^{131}$I activity and measurements are performed in an accurately calibrated (for $^{131}$I) well counter. To determine the whole-body activity, serial measurements are performed with either a dual head gamma camera or a scintillation probe. Once time integrated activities (cumulated activities) for both blood and whole-body are determined from the serial measurements, the absorbed dose to the blood per unit administered activity (i.e. Gy/GBq administered activity) can be determined using the S-value based equations of the MIRD schema. The therapeutic $^{131}$I activity that can be safely administered while maintaining blood radiation absorbed dose ≤ 2 Gy) can then be determined based on this pre-therapy predicted radiation absorbed dose to the blood. (157) Further restrictions to MTA recommend that the administered therapeutic activity does not exceed 4.44 GBq (120 mCi) $^{131}$I whole-body retention at 48 h, or 3 GBq (80 mCi) $^{131}$I whole-body retention at 48 h if pulmonary metastases are present. (155) The limitation of the blood-dosimetry method for treating to the MTA is the lack of information regarding the radiation absorbed dose to the targeted metastatic lesions, which can lead to over- or under-therapy.

The goal of lesion-based dosimetry is calculation of individualized $^{131}$I therapeutic activity that would deliver sufficient radiation absorbed dose to target for achieving maximum therapeutic effect, while minimizing the risk for side effects on non-target tissues. In this calculation, the time integrated activity from serial quantitative imaging using a tracer amount of $^{131}$I can be used with the MIRD schema to determine the predicted lesion absorbed dose per unit administered activity considering only the dominant self-irradiation component of the total absorbed dose. However, to date there is no validated method to determine the remnant or metastatic tissue mass, which gives high uncertainty to the lesion-dosimetry. The uncertainty in the dosimetry calculations can be noted in the studies that have reported on absorbed dose thresholds for providing therapeutic efficacy. For instance, Maxon et al proposed a value of 300 Gy to thyroid remnants and 80 Gy to lymph nodal metastases,(158) Flux et al. a value of at least 49 Gy to thyroid remnants, (159) and Wierts et al. a value of 90 Gy to thyroid remnants and 40 Gy to lymph nodal metastases. (160)
Radioiodine Toxicity: Acute and Chronic Side Effects of Radioiodine Therapy

Radioiodine Toxicity: Acute and Chronic Side Effects of Radioiodine Therapy

131I sodium iodide carries the risk of several adverse events, which - while uncomfortable and sometimes chronic -, are rarely lethal to the patient receiving the therapeutic activity. Oral 131I is rapidly absorbed in the stomach and duodenum, and concentrated in the thyroid tissue, salivary and lacrimal glands, and in the breast tissue during pregnancy and lactation (estrogen-priming of transient NIS expression in ductal epithelial cells). This occurs through the action of the NIS, a plasma membrane glycoprotein which transports the monovalent iodide anion against a concentration gradient into specialized cells of these organs and glands. The emitted beta particles cause cellular damage which, if enough radiation enters the cell, will not be reparable. This is why 131I is employed to selectively treat thyroid cancer. However, 131I has sublethal and lethal effects on the cells of other organs and glands that concentrate it, resulting in side effects of 131I therapy.

Acute 131I toxicity

Numerous salivary glands concentrate 131I rapidly, including the paired submandibular, submaxillary, and parotid glands (the tubarial glands, just discovered in 2020, may represent a fourth set), as well as several hundred 1 - 2 mm diameter salivary glands in the buccal, labial, and lingual mucosa, hard palate, floor of the mouth, tongue, and throat. Because of the iodine-concentrating glands throughout the mouth, as well as from secreted radioactive saliva, painful stomatitis and glossitis may also occur in up to 20% of patients.

Acute sialadenitis characterized by pain and swelling of the salivary glands occurring within 48 hours of 131I therapy has been reported in 13 - 50% of patients. (161, 162) The risk of salivary gland dysfunction increases with higher 131I therapeutic activities (>3.7 GBq [100 mCi] for xerostomia; > 5.5 GBq [150 mCi] for sialadenitis). (148) However, the incidence of these salivary gland and oral adverse reactions can be ameliorated to as low as 1 - 5% by prolonged salivary stimulation and scheduled multiple efforts at washing out the mouth with water over several days. (163) Van Nostrand et al. (164) and Kulkarni et al. (165) have demonstrated in retrospective and prospective studies that the radiopharmacokinetics of radioiodine in the parotid glands change minute-to-minute with rapid clearance of activity after salivary stimulation and then rapid subsequent re-accumulation that can be aborted with continuous and prolonged salivary stimulation.
Protective measures to minimize acute salivary side effects consist of hydration, the use of lemon candies or lemon juice and salivary gland massage with the goal of stimulating salivary drainage and decreasing radiation absorbed dose to the salivary glands, however the optimal time to start, frequency and duration of salivary gland stimulation are not standardized. (148) Several reports suggested that the early use of sialagogues may be counterproductive making the topic of salivary stimulation controversial; however, the data are heterogeneous and do not withstand scientific scrutiny. In particular, the study by Nakada et al. reported a significant increase in acute sialadenitis (63.8 vs. 36.8%) and subjective xerostomia (23.8 vs. 11.2%) in patients who were administered sialagogues within 24 hours of $^{131}$I therapy as compared with a group of patients in whom sialagogue administration was delayed for 24 hours after $^{131}$I treatment; however, the salivary stimulation protocol was not published and consistency of sialagogues stimulation is unknown; although sialagogue administration was delayed for 24 hours, it is unclear if the patients did it once or more times. (166) The authors’ presumed mechanism for the higher incidence of sialadenitis in the patients who received sialagogues was an increased blood flow resulting in increased $^{131}$I delivery to the salivary glands during stimulated salivation. However, a subsequent prospective study of $^{123}$I radiopharmacokinetics after sialagogue administration in patients who served as their own control and underwent salivary $^{123}$I scans with, - and without, - lemon juice administration demonstrated that such postulated increased radioiodine delivery after stimulated salivation does not occur, and in fact sialagogue administration reduced the potential radiation absorbed dose to the salivary glands by a mean relative decrease of 34.2% as compared to the non-stimulated state. (165) Jentzen et al. reported $^{124}$I PET/CT salivary gland dosimetry results for 2 separate groups (10 patients each), studied with, -and without,- sialagogues stimulation in the first 24 hours after $^{124}$I administration. In the salivary stimulation study the patients were prepared predominantly by hypothyroid stimulation protocol (8/10 patients underwent THW) and chewed on lemon slices throughout the first day starting at ~ 20 min. after oral $^{124}$I capsule intake. The calculated mean organ absorbed dose per administered activity (ODpA) was $0.32\pm0.13$ (0.18–0.55) Gy/GBq for the submandibular glands and $0.31\pm0.10$ (0.13–0.46) Gy/GBq for the parotid glands. The authors concluded that the salivary radiation absorbed dose after $^{131}$I therapy is too low to account for the radiation-induced damage, which is expected to occur at ODpA ~ 5 Gy/GBq as estimated by comparing dose-response relationships from external beam radiation therapy, and that non-uniform activity
distribution within the glands, primarily involving the salivary duct epithelium probably plays a role. (167)

In a subsequent paper the authors reported $^{124}$I salivary dosimetry results in a group of patients studied without salivary stimulation, who were prepared either by rhTSH injection or THW. However, the precise distribution of preparation method within the group was not reported. The calculated mean ODpA was 0.25±0.06 (0.17–0.39) Gy/GBq for the submandibular glands and 0.22± 0.05 (0.16–0.3) Gy/GBq for the parotid glands. (168) Comparing these results with the prior dosimetry results obtained in the salivary-stimulation study (167), the authors concluded that the mean ODpA (averaged over both parotid and submandibular salivary glands) in the nonstimulation group was reduced by 28% compared to the mean ODpA in the stimulation group. (168) However, direct comparison with the salivary stimulation group in which 80% patients received THW is not possible due to the following considerations: 1) the recognized difference between hypothyroid- vs. rhTSH stimulation in $^{131}$I residence times and organ dosimetry, 2) the lack of specific details regarding the number of patients receiving rhTSH vs. THW preparation in the salivary nonstimulated group and 3) measurements of radioactivity within salivary glands were performed at 4, 12, and/or 24 hours rather than minute by minute.

In substantiation that the observed difference between salivary stimulated and nonstimulated groups is due to the difference between hypothyroid- vs rhTSH stimulation in $^{131}$I tissue residence times, the $^{124}$I salivary dosimetry results reported by Jentzen et al. in the salivary nonstimulated group (168) are similar to the results reported by Kolbert et al. in a group of 26 patients prepared exclusively by rhTSH administration, with reported mean salivary ODpA ranging between 0.19 – 0.26 Gy/GBq. (169) Preparation by rhTSH stimulation results in lesser radiation absorbed doses to normal organs (including the salivary glands) due to faster $^{131}$I clearance in euthyroid state as compared to hypothyroid state, therefore definitive conclusions about the salivary gland effects of lemon stimulation cannot be reached based on published $^{124}$I salivary dosimetry data obtained in different patient groups.

Van Nostrand et al. demonstrated in a subsequent study of $^{123}$I kinetics in the parotid glands that the estimated percent reduction in radiation absorbed dose to the salivary glands ranges between 37 – 47% after sialagogue administration. (164) The radiopharmacokinetics of radioiodine in the salivary glands is minute-by-minute and although it remains controversial whether there is benefit in withholding sialagogues
for the first 24 hours, there is strong evidence that continuous sialagogues administration beginning shortly after $^{131}$I therapy and continued through the first several days (and nights), significantly reduces the radiation absorbed dose to the salivary glands. (163, 170)

*Dysgeusia* (taste dysfunction) results from damage of the small mucous salivary glands in the vicinity of the taste buds and is a temporary side effect of $^{131}$I therapy lasting several weeks post-treatment. (171)

*Radiation gastritis* and *enteritis* are not uncommon from radiation damage to the mucosa of the upper gastrointestinal tract, causing anorexia, nausea, and occasional emesis with an incidence as high as 30%. (172) Nausea and vomiting can be largely prevented by oral selective serotonin receptor (5-HT3) antagonists, which peripherally stimulate vagal nerve terminals of the gastrointestinal tract and centrally react with receptors in the area postrema of the fourth ventricle. If post-therapy emesis occurs just hours after $^{131}$I ingestion, the treating physician does not know how much of the therapeutic activity was absorbed but cannot immediately retreat, as cumulative $^{131}$I toxicity from the two administrations may occur.

*Radiation thyroiditis* is a serious but uncommon complication following relatively large $^{131}$I therapeutic activities, occurring when the patient's attempted total thyroidectomy has been inadequate to remove virtually the entire gland. This form of thyroiditis can be quite painful, and the residual tissue may swell significantly, rarely compromising the upper airway. This is another reason that post-operative diagnostic scintigraphy should be performed prior to therapeutic $^{131}$I administration to exclude this possibility. Therefore, an elevated neck $^{131}$I uptake value such as 8-10% requires great care in administering $^{131}$I therapy. Furthermore, one should be cautious in administering $^{131}$I therapy to a patient with high neck $^{131}$I uptake exceeding 10-15%, and in such cases the decision for treatment should be based on factors such as the number of foci, radioactivity concentration per focus of uptake, and an estimate of the target volume of treatment based on ultrasound and/or SPECT/CT imaging. Completion thyroidectomy, or $^{131}$I ablation of the remaining thyroid lobe should be performed before $^{131}$I therapy can be safely administered in such cases. (79, 173)

**Chronic $^{131}$I toxicity**

Chronic adverse effects of $^{131}$I therapy may occur weeks, months, or even years post-therapy. The threshold for the induction of permanent sterility in humans is 3.5 Gy for the testis and 2.5 Gy for the ovary.
The oocytes are formed in the ovary prenatally and primordial oocytes are relatively resistant to low radiation dose scattered from the bladder, therefore fertility is generally unaffected by $^{131}$I therapy in young women. (174) However, male fertility may be seriously reduced because highly radiosensitive sperm in the testes are exposed to significant radiation from the bladder after therapy, especially at activities in excess of 3.74 - 5.6 GBq (100 - 150 mCi). (175) The spermatogonia are among the most radiation sensitive tissues in male mammals. (176, 177) Following $^{131}$I therapy for DTC, the testis receives radiation not only from proximity to the bladder but also because the germinal and Leydig cells of the testis express the NIS which concentrates iodide ion. (178) In a series of 40 young men treated for DTC, sperm counts decreased by 3 months after therapeutic $^{131}$I activity of 3.7 GBq (100 mCi), returning to normal by 13 months. (179).

Multiple courses of $^{131}$I therapy raise the risk of oligospermia up to 50%, (180) while in another study sperm DNA fragmentation persisted up to 28 months following a second $^{131}$I therapy. (181) After multiple therapeutic $^{131}$I administrations the number of normokinetic sperm showed a consistent reduction. (182) Based on this data it is recommended that for patients considered for high $^{131}$I therapeutic activities $\geq 7.4$ GBq ($\geq 200$ mCi) and who anticipate fertility, sperm storage should be considered before $^{131}$I therapy. If sperm analysis returns to normal after 1 year of $^{131}$I therapy, then the specimen is discarded. There is agreement among the sources cited above that if multiple $^{131}$I therapies are required, sperm storage for males desiring fertility should be offered, at least before the second $^{131}$I therapy. (180-182). Aggressive hydration for several days following $^{131}$I therapy ($> 4$ L [1 Gal] daily fluid intake) is recommended for diluting excreted $^{131}$I in a large volume of urine and increasing urination frequency, with the goal of reducing scattered radiation from the bladder to adjacent gonads.

*Chronic xerostomia* and *chronic painful sialadenitis* with sialolithiasis can result from salivary gland radiation in about 10% of patients. (163) (183) In addition, $^{131}$I accumulation in the lacrimal glands after therapy can uncommonly lead to destruction of the lacrimal tissue and resultant *xerophthalmia.*

*Epiphora* secondary to lacrimal system damage and subsequent local fibrosis can occur because of $^{131}$I uptake and retention in the tear ducts due to NIS expression in the epithelial cells of the lacrimal sac and nasolacrimal duct, as well as radioactive tears draining into the nose following administration of $^{131}$I therapeutic activities in excess of 5.6 GBq (150 mCi). (183) High intranasal $^{131}$I accumulation was demonstrated on PT-WBS in 4% of patients receiving therapeutic activities $\geq 5.6$ GBq (150 mCi), and high
nasal $^{131}$I uptake noted on post-therapeutic scintigraphy can be a predictor for toxicity to the lacrimal drainage system and possibly subsequent development of nasolacrimal duct obstruction. (184)

Dacryoscintigraphy or dacryocystography are used for determining the specific location of nasolacrimal obstruction and guiding ophthalmologic treatment by stent deployment and/or dacryocystorhinostomy. For patients experiencing salivary or lacrimal symptoms after $^{131}$I therapy, early timely referral for specialized treatment is recommended for preservation of glandular function. (148)

High-activity $^{131}$I therapy in patients with distant pulmonary metastatic disease carries a risk of radiation-induced pneumonitis and lung fibrosis when excessive $^{131}$I activity is retained in the lungs. Simplified dosimetry methods to limit the potential for lung tissue damage following $^{131}$I treatment have been developed to mitigate the serious toxicity risk. (185) (186) Progressive pulmonary fibrosis has been reported following repeated $^{131}$I therapy in 7% of children with thyroid cancer metastatic to the lungs. (187) Bone marrow suppression may be seen in pediatric thyroid cancer patients treated with 5.6 - 7.4 GBq (150 - 200 mCi) of $^{131}$I, but usually with limited clinical significance. (188) However, to avoid significant pancytopenia, especially in older patients with extensive metastatic thyroid cancer requiring larger $^{131}$I therapeutic activities, blood dosimetry becomes an important part of therapy planning to avoid radiation absorbed dose to blood (a surrogate of bone marrow dose) in excess of 2 Gy. (155, 157)

The lactating breast concentrates iodine, which has important implications for the nursing mother and her infant. In one study, following the therapeutic administration of 4 GBq of $^{131}$I to a healthy mother during lactation, the breast received 1.6 Gy. The time after receiving radioiodine therapy (and discontinuing lactation) required for the infant both to receive an effective dose < 1 mSv and thyroid dose < 10 mSv was calculated to be least 52 days. Therefore, a lactating mother requiring $^{131}$I therapy must cease nursing her newborn child. (189) $^{131}$I administration needs to be postponed for several months for allowing physiological breast tissue involution after lactation. (190) $^{123}$I scintigraphy can be performed to help confirm breast tissue involution and functional suppression of NIS expression in mammary glands by demonstrating lack of $^{123}$I uptake within the breast. (191)
Risk of Subsequent Primary Malignancies after $^{131}$I Therapy for DTC

The issue of second primary malignancies following $^{131}$I therapy for DTC has been a controversial topic. Based on the clinical observations after exposure to external radiation therapy, latent periods for radiation-induced cancer have been defined, which are also presumed to apply to $^{131}$I therapy. The minimum latent period is 2 years for leukemia, and 4-5 years for most solid tumors. (192) The peak latent period for induction of leukemia is 5-7 years. (193) Mean latent period for leukemia is 7-10 years and for most solid tumors is generally 10-30 years. (192). The range of the latent period for solid tumors is 10 - 60+ years. (193). No definite threshold for administered $^{131}$I activity as an etiology of a second primary malignancy has been identified at this time. Minimum follow-up for detection of radiogenic-induced malignancy should probably be at least 10 years. Second primary malignancies identified prior to 4 years post $^{131}$I therapy should be presumed to be co-incidental and not related to $^{131}$I therapy. (192)

Several studies found no evidence of increased incidence of second primary malignancy (solid tumors or leukemia) in thyroid cancer patients treated with $^{131}$I. (194-198) Mean follow up for these studies were: 11 years (194), 10.6 years (197), 10 years (196), and approximately 5 years. (195)

Leukemia - Several studies found no statistically significant increased risk of leukemia after $^{131}$I therapy. (195, 196, 199, 200) Studies by Rubino et al. (201) and Reiners et al. (202) found a slightly increased incidence of leukemia. Rubino et al. evaluated three large cohorts of Swedish, French and Italian patients and found an excess of 3 cases of leukemia per 10,000 patients (0.03%; RR = 2.5). (201) Sawka, et al. also found a mildly increased incidence of leukemia with a RR of 2.5 (203)

Salivary gland cancers - There is a small but apparently real increased incidence of salivary gland cancers due to $^{131}$I therapy. Rubino et al. found a small but increased incidence of salivary gland cancers, with an increasing risk related to increasing administered activity: in a cohort of 6841 patients there were six cases of salivary cancer in patients who received $^{131}$I therapy versus one case in patients not treated with $^{131}$I. (201) Marti et al. found a mildly increased incidence of salivary gland cancers in pediatric and young adult patients treated with $^{131}$I, slightly increased compared to adult patients. [ SIR = 34.1, p=0.0007, 1.7 cases per 10,000 PYR]. (200)
Breast cancer – There appears to be a bi-directional association of DTC and breast cancer, meaning that the risk of breast cancer is increased in patients with DTC and vice versa. (204) The increased incidence of breast cancer in DTC survivors is independent on whether $^{131}$I therapy was administered for DTC treatment. (202) Women with a history of thyroid carcinoma have a greater than expected risk of developing breast cancer, this risk being most pronounced in premenopausal white women. (198) Premenopausal women (age 20 - 49 years) with an index DTC diagnosis have a significantly increased risk of developing subsequent breast carcinoma (RR= 1.42; $P = 0.001$), while women with index breast cancer do not have an increased risk for DTC. (205) A SEER analysis of 30,278 patients followed for nearly 30 years showed that both the $^{131}$I therapy group and the non-irradiated group had significantly elevated risk for breast cancer as expected in the general population, but the relative risk was statistically indistinguishable between the 2 groups. This suggests that the increased risk of breast cancer is likely due to other factors. (206) The cause of this association between thyroid cancer and breast cancer remains unclear, however, it is noted that both are endocrine tumors. (205, 207) In an extensive analysis performed in 2020 Reiners et al. concluded that $^{131}$I therapy for thyroid cancer did not increase the risk of breast cancer. (202)

It is important to note that the lactating breast concentrates $^{131}$I due to high endogenous estrogen/progesterone levels during late pregnancy and lactation which prime the ductal epithelial cells for transient functional expression of NIS for providing an adequate supply of iodine in the breast milk for thyroid hormone synthesis by the newborn to support growth and development. Therefore, it is particularly important to ensure that sufficient time is allowed for breast tissue involution after cessation of lactation prior to proceeding with $^{131}$I therapy. In the absence of pregnancy and lactation NIS is either not expressed at all or present in an inactive form in the normal breast tissue. (208) However, several studies demonstrated NIS upregulation in breast cancer. (209, 210)

Other solid tumors – After a mean follow up of 13 years Rubino et al. found a slight excess of 53 solid tumors per 10,000 patients over 10 years, per administered activity of 3.7 GBq (100 mCi). (201) De Vathaire et al. found an increase in colon cancer but no other types of cancer. [ERR = 0.5 per GBq, $P=0.02$]. (211) After a mean follow up of 8.6 years Brown et al. found an increase in some tumors, including some that are considered radioresistant (e.g. brain bone and connective tissue tumors) (192), but
not others including the GI tract. In this cohort 7.1% of patients evaluated for thyroid cancer developed second primary malignancies, however the greatest limitation of this study is that the time allowed for latent period after $^{131}$I therapy was only 2 months. Increases in cancer diagnosis were seen up to 10 years post $^{131}$I therapy, but not later. Administered $^{131}$I activities were not known. (206)

Overall, the incidence of salivary gland cancers and leukemia is small but real. Increased incidence of breast cancer from $^{131}$I therapy for thyroid cancer has not been demonstrated. Increased incidence of other solid malignancies is seen in some studies but not in others. Verkooijen et al. suggests that there may be a common etiologic or genetic mechanism instead of a causal relationship. (197)

**THYROID HORMONE THERAPY AND SURVEILLANCE STRATEGY**

After $^{131}$I therapy patients receive levothyroxine (L-T4) therapy with the goal of TSH suppression depending on the patients' risk stratification (0.1 - 0.3 mU/L for patients with regional metastases and < 0.1 mU/L for patients with distant metastases). (6) A recent consensus statement by the American, British and European Thyroid Associations recommends that L-T4/L-T3 therapy should be considered under specific circumstances and for selected patients, especially hypothyroid patients without residual thyroid function and those with persistent symptoms of impaired well-being and cognitive dysfunction despite adequate L-T4 doses. (212)

Serum Tg measurement is employed for monitoring DTC status after primary therapy. However, the usefulness of following Tg is limited in patients who have anti-Tg antibodies (TgAb) because the serum Tg levels can be underestimated when using immunometric assays. (52) In these patients the trend of TgAb levels over time can serve as a surrogate tumor marker (29). Immune memory in patients with a background of thyroid autoimmune disease accounts for the slow decline of TgAb levels after initial DTC treatment, and levels should be interpreted with caution for at least 6 months after $^{131}$I therapy. (51) During long-term surveillance the TSH-suppression target is adjusted taking into consideration the outcome of primary therapy according to dynamic risk restratification: in patients with a structural incomplete response serum TSH is maintained < 0.1 mIU/L indefinitely, while target values of 0.5 - 2 mIU/L and 0.1 - 0.5 mIU/L are adopted in low- to intermediate-risk, and high-risk patients with excellent response, respectively. Finally, TSH target
values of 0.1 - 0.5 mIU/L are also suggested when post-therapy Tg remains detectable with evidence of structural disease. (6)

RESPONSE ASSESSMENT AFTER PRIMARY THERAPY

Dynamic risk re-stratification consists of reassignment of recurrence risk based on response to initial treatment, which is predictive of long-term clinical outcomes. (6) This is performed during the first 2 years of follow-up after initial therapy (total thyroidectomy followed by $^{131}$I therapy) and involves basal and stimulated thyroglobulin (Tg) testing and imaging reevaluation. US is a reliable method for detection of loco-regional persistent or recurrent DTC (i.e., thyroid bed and cervical lymph nodes). However, the probability of false positive results leading to unnecessary and expensive additional procedures is far from negligible. Accordingly, the use of US should be limited (particularly in low-risk DTC) and, in the absence of TgAb, reserved only for patients with unstimulated serum Tg levels $\geq 1$ ng/mL. (103) US-guided fine needle aspiration (FNA)-biopsy with Tg determination in the fluid aspirate is used for diagnostic confirmation of residual disease in suspicious-appearing cervical lymph nodes identified on anatomic imaging.

In combination with Tg measurement, follow-up DxWBS are helpful for therapy response evaluation and to identify patients with suspected non-iodine avid metastatic disease (based on elevated basal and/or stimulated Tg and negative WBS), which will prompt further investigation with $^{18}$F-FDG PET/CT and/or diagnostic CT scan for localizing structural persistent disease. (73, 213, 214) The combination of Tg, US and follow-up DxWBS performed at 1 - 2 years after primary therapy is used to re-stratify the risk of recurrence according to the patient’s response to initial therapy for more accurately predicting long-term clinical outcomes. The risk re-stratification criteria are summarized in Table 4. (6)

In patients with excellent response to therapy the risk of disease recurrence is 1 - 4%, which for intermediate-risk patients (whose initial risk for recurrence is estimated at 36 - 43%) and for high-risk patients (whose initial risk for recurrence is estimated at 68 - 70%) represents a major change in risk when complete response to therapy is achieved. The clinical outcomes in patients with biochemical incomplete response are usually good: approximately 60% have no evidence of disease over long-term follow-up; 20% patients continue to have persistently abnormal Tg values without structural correlate, and only 20% patients
develop structurally identifiable disease over 5 - 10 years follow-up. Patients with biochemical indeterminate response do generally well: in 80 - 90% of patients the nonspecific biochemical findings either remain stable or resolve over time with L-T4 suppression therapy alone; however, up to 20% of these patients will eventually develop functional, or structural evidence of disease progression and require additional therapies. Patients with structural incomplete response require a multidisciplinary management tailored to their disease status (e.g. regional vs. distant metastases; iodine-avid vs. non-iodine avid disease). (6); depending on the results of such additional treatment patients may be re-stratified according to the criteria above. See Table 4 for dynamic risk stratification criteria used to assess treatment response. Importantly, the dynamic risk re-stratification has been validated only in patients treated with complete thyroid ablation (i.e. [near-] total thyroidectomy and post-operative $^{131}$I therapy). Evidence is not available for patients treated with lobectomy alone, or with thyroidectomy without post-operative $^{131}$I therapy. (215) After thyroidectomy, Tg levels are influenced by the amount of thyroid tissue remnant and the TSH level at the time of Tg measurement. Even if decreasing Tg levels may be reassuring, it is difficult to provide general interpretation criteria for serum Tg in such cases. Furthermore, measuring Tg is essentially useless after lobectomy as Tg levels will not depend on the presence or absence of tumor, but rather on the mass of remaining thyroid tissue, current iodine status and TSH concentration. (216) Park and colleagues followed 208 low-risk papillary thyroid carcinoma patients post lobectomy over a median of 6.9 years: the levels of Tg and Tg/TSH ratio, and the proportions of patients in whom serum Tg levels increased by $\geq$ 50%, or by $\geq$ 100% over baseline measurement, did not differ significantly in patients with or without recurrence. (217)

**THERAPY OF ADVANCED DISEASE**

Distant metastases develop in about 10% of DTC patients, commonly in lungs, and less frequently in bone, brain, liver and skin, and are the main cause of significant symptoms and death (i.e. overall mortality of 65% at 5 years and 75% at 10 years). (218) Younger patients and those with single-organ metastases and low disease burden have the best outcome. (60) The mainstay of metastatic disease treatment is TSH suppression and repeated courses of $^{131}$I treatment as long as the disease remains iodine-avid. (219) About two-thirds of patients have radioiodine-avid distant metastases and more than 40% of the latter will achieve
remission after $^{131}$I treatments. However, a minority of DTC cases loses the ability to concentrate iodine in sufficient quantities to allow therapeutically effective radiation absorbed doses to DTC lesions (i.e., radioiodine-refractory DTC). Determining when a patient will no longer respond to $^{131}$I therapy can be challenging, and all factors impacting the patient’s specific clinical situation such as age, tumor histology, initial stage, radioiodine residual avidity, $^{18}$F-FDG avidity should be carefully considered. Definitions of radioiodine refractory DTC have been proposed by several authors, followed by updated classifications of radioiodine refractory disease. Classification of a patient as radioiodine refractory is very important and consequential. If one classifies a patient as radioiodine refractory when in fact the patient may respond to an $^{131}$I therapy, then that patient has lost the potential benefit of an effective $^{131}$I therapy in a situation with limited therapeutic options. However, if patients receive $^{131}$I therapy without benefit, not only may these patients experience unnecessary side effects from an ineffective therapy, but they are also not receiving an alternative therapy that could be beneficial.

In regard to various proposed classifications of radioiodine refractory disease, the criterion with the best predictive value that a patient has radioiodine refractory disease and will not respond to another $^{131}$I treatment is the patient progressing after a short time interval after the administration of a maximum safe $^{131}$I therapeutic activity. All other criteria will have varying degrees of likelihood that the patient is radioiodine refractory, and these criteria should be cautiously considered with particular attention regarding their limitations. Although exact likelihood ratios cannot be given herein for the various criteria that have been used in the past, Figure 5 presents an example of the spectrum of relatively low to high likelihoods of three criteria for predicting that a patient’s metastatic DTC is radioiodine refractory. Nevertheless, the time from $^{131}$I treatment to progression (i.e. progression free survival) after optimized $^{131}$I treatment is one of the most important criteria for predicting radioiodine refractory DTC. Although in the past disease progression was considered in and of itself indicative of $^{131}$I treatment failure, progression must be considered in light of many factors as shown in Table 5, including length of progression free survival and the amount of $^{131}$I activity administered. Caveats guiding the classifications of a patient’s metastatic DTC as radioiodine refractory are also noted in Table 6. Additional management options to be considered prior to classifying a patient’s metastatic DTC as radioiodine refractory are presented in Table 7.
Despite a negative DxWBS, administration of $^{131}$I therapy should still be considered, and a PT-WBS should be performed. Although absence of uptake on a PT-WBS is a stronger indicator of radioiodine refractory disease, it is not a definitive imaging biomarker for tumor NIS expression in the setting of progressive metastatic disease. Several authors have shown that the timing of a PT-WBS scan after the therapeutic $^{131}$I administration (e.g., 3 - 4 days versus 5 - 7 days) can make the difference in interpretation between a negative and positive PT-WBS. (80, 81, 83, 84, 227) Additional options to be considered before classifying a patient’s DTC as radioiodine refractory are: 1) refer the patient to a site that performs radioiodine dosimetry and/or frequently manages aggressive and progressive DTC, or 2) help selected patients explore eligibility for participating in a research study offering “re-sensitizing” or “redifferentiating” agents to determine if radioiodine uptake can be re-established or increased for a potential $^{131}$I therapy as described by Ho et al. (228), Jaber et al. (229), Tepmongkol et al. (230) and Rothenberg et al. (231)

Focally-targeted treatment (i.e., resection, vertebroplasty, external beam radiation therapy and thermal ablation) can provide local control, provide symptomatic relief and delay initiation of systemic therapy. These therapies can be used with concurrent $^{131}$I or other systemic therapies when targeting progression in a single lesion in addition to systemic therapy may enable continued overall disease control. (232) Treatment with bisphosphonates or denosumab can delay time to skeletal related events. (233)

However, caution is necessary if using biphosphonates as there is a risk for osteonecrosis of the jaw, especially in patients treated with intravenous bisphosphonates (OR 4.27). Therefore, it is important to evaluate dental health before initiation of the therapy and avoid dental procedures during the therapy. (234)

In cases of confirmed systemic progression of radioiodine refractory disease, intravenous chemotherapy with doxorubicin was traditionally used, but a partial response was obtained only in a small minority of patients.

More recently “targeted” therapies, including the multikinase inhibitors (MKI) (e.g., sorafenib and lenvatinib) have been approved by the US Food and Drug Administration and European Medicines Agency for patients with advanced radioiodine refractory DTC. These drugs have been shown to induce periods of progression-free survival (rarely remission). However, they do not increase cancer-specific survival and may be associated with significant side effects, such as hypertension, diarrhea, hand/foot skin reactions, rash, fatigue, mucositis, loss of appetite, and weight loss. (218) It remains unclear which patients will benefit from MKI in terms of an increase in quality adjusted life years and the optimal time to start therapy, especially in
asymptomatic patients. As a rule, molecular targeted therapies should be started in patients with progression of measurable lesions (as defined radiologically by RECIST criteria) over the previous 12 months, taking into consideration tumor burden, disease sites, symptoms, and the risk of local complications. (235) In the setting of clinical trials involving redifferentiation strategy, molecular tumor analysis can direct therapy (e.g., BRAFV600E → dabrafenib [+/- trametinib, vemurafenib; BRAF- → trametinib]). Furthermore, identification of NTRK, RET fusion could also direct therapy toward selective inhibitors e.g. selpercatinib.

The biological mechanisms implicated in radioiodine refractoriness involve gain-of-function mutations in the MAPK signaling pathway, resulting in reduced NIS and other iodine-metabolizing genes expression. Experimental data showed that MAPK signaling pathway inhibition using MEK or BRAF inhibitors may restore radioiodine avidity. Subsequent clinical studies demonstrated that mutation-guided treatment using selective MEK inhibitors (selumetinib, trametinib), BRAF inhibitors (dabrafenib, vemurafenib), or a combination of BRAF inhibitor and MEK inhibitor, is feasible and represents a promising strategy to redifferentiate radioiodine refractory DTC, thereby permitting reapplication of $^{131}$I therapy. Preliminary data obtained on a small clinical series of 13 patients demonstrated restoration of $^{131}$I avidity in 62% of patients who subsequently received $^{131}$I treatment [median activity 7.6 GBq (204.4 mCi), range 5.5 – 9.4 GBq (150 - 253 mCi)], resulting in durable disease control (median duration > 1 year) while not receiving chronic, expensive multikinase inhibitor therapy. (229) $^{131}$I therapy remains the only known cure for metastatic radiiodine-sensitive DTC and the use of a redifferentiating strategy to permit additional $^{131}$I treatment for patients with radiiodine-refractory metastatic disease represents a promising therapeutic approach while minimizing exposure to kinase inhibitor therapy.

$^{18}$F-FDG PET/CT Imaging for Thyroid Cancer

Advances in molecular diagnostic imaging and the clinical availability of PET/CT systems produced a paradigm shift in the management of thyroid cancer by allowing characterization of tumor biology based on variable uptake patterns of radioiodine and $^{18}$F-FDG in metastatic lesions. Feine et al. described the “flip-flop” phenomenon as opposite radiotracer uptake pattern on radioiodine scintigraphy and $^{18}$FDG-PET/CT imaging, recognizing 4 patterns of variable radioiodine/FGD uptake in metastatic disease. **Type I pattern** is characterized by negative $^{131}$I/positive FDG uptake and it is the most commonly encountered pattern in
patients with elevated Tg and negative scintigraphy (i.e. Tg+/scan-), which is found in approximately 46% cases. **Type II pattern** is characterized by positive $^{131}$I/negative FDG uptake and it represents the most favorable context for therapeutic $^{131}$I administration. **Type III pattern** consists of a combination of type I and II patterns recognized in different metastatic lesions within the same patient due to varying biological behavior in metastatic foci. **Type IV pattern** is characterized by uptake of both $^{131}$I and for $^{18}$FDG within same metastatic lesions. (236, 237) The flip-flop phenomenon is not a constant for DTC metastases but rather a variable marker of tumor biology. A prospective study of 122 post-thyroidectomy patients with established metastatic DTC who were imaged with both DxWBS and $^{18}$FDG-PET/CT showed a general correlation of FDG-avidity with lack of iodine avidity; however, the correlation coefficient was only 0.62.

For the selected SUVmax cut-off value of 4.0, the authors calculated a sensitivity of 75.3% and specificity of 56.7% for identification of non-iodine avid metastatic disease. (238) Hence, the decision on whether to perform $^{131}$I therapy or not should not be based on $^{18}$FDG-PET/CT alone. The most common application of PET/CT imaging in DTC is for evaluation of patients with elevated thyroglobulin and negative DxWBS (i.e. Tg+/scan-). (239)

**Management Algorithm for patients with elevated Tg and negative DxWBS (Tg+/scan-)**

Although this is frequently seen as one syndrome (called TENIS syndrome, i.e. thyroglobulin elevation, negative iodine scintigraphy), in fact it represents a wide spectrum of clinical situations. For example, the spectrum may extend from a 30-year-old patient who is 1) status post $^{131}$I remnant ablation, 2) has a stable low-level nonstimulated Tg (e.g. 4 ng/ml) without interfering TgAb, 3) has a negative follow-up DxWBS and 4) is considered as low-risk for disease recurrence to the opposite end of the spectrum of a 60-year-old patient who has 1) significantly elevated nonstimulated Tg (e.g. 50 ng/ml), 2) rapid Tg doubling time (Tg-DT) less than 1 year and 3) negative DxWBS. Accordingly, the management of these two patients may be very different, and the development of guidelines for the various patient clinical situations is challenging. However, the development of a treatment plan may be facilitated by following four steps: 1) rule out false negative WBS and false positive thyroglobulin levels, 2) perform patient risk re-stratification, 3) obtain non-radioiodine imaging, and 4) customize management to the location and number of the metastatic lesions.
**Step 1: Rule out false negative DxWBS and false positive Tg levels**

To evaluate for false negative DxWBS, the interpreting physician needs to consider the following: 1) screen for a history of recent iodine load, such as recent administration of radiologic contrast agents or ingestion of kelp, as well as administration of amiodarone, even months to years earlier; 2) confirm compliance with low iodine diet as demonstrated by low urinary iodine levels (e.g. spot urine iodine level, spot urine iodine to creatinine ratio, or 24-hour urine iodine collection); 3) ascertain adequate TSH elevation, which is especially important with preparation by thyroid hormone withdrawal; 4) exclude heterophilic antibody interference on Tg measurement (prevalence 0.4-1%) (240); 5) confirm correct radiopharmaceutical administration (reviewing documents for appropriate isotope and prescribed activity and reviewing the scan images themselves for inappropriate distribution of radioactivity); 6) confirm technical scan parameters (collimator type, peaking of energy window, table speed for planar scan and time interval for stop position for SPECT acquisition, etc). Although one may assume that all radioiodine scans are performed equally, they are not, and assessment of the quality of the scan is important to minimize false negative radioiodine scans. (241)

**Step 2: Perform dynamic risk restratification**

If the patient has a low risk for disease recurrence (such as the first patient described above), then perhaps active surveillance is appropriate, and active surveillance may include 1) physical exam, 2) Tg, TgAb and TSH testing, and 3) US of the thyroid bed and neck. However, if the patient has an intermediate or higher risk for disease recurrence, then non-radioiodine imaging is indicated. Other factors such as noted in Table 8 may be relevant to consider.

**Step 3: Obtain non-radioiodine imaging**

Non-radioiodine imaging studies for metastatic DTC have been divided into three tiers: primary, secondary, and tertiary. The primary tier includes: 1) neck US, 2) $^{18}$F-FDG PET/CT imaging, and/or 3) CT of the neck, chest, abdomen and pelvis. These studies can be performed sequentially; however, whenever possible, integrated PET/CT imaging is preferable because it provides both functional and anatomic information. The secondary tier includes: 1) brain MRI; 2) bone scanning (using $^{99m}$Tc methylene disphosphonate [$^{99m}$Tc MDP] or $^{18}$F Sodium fluoride PET-CT [$^{18}$F-NaF-PET-CT]), and 3) mitochondrial
imaging (e.g., $^{99m}$Tc-sestamibi, $^{201}$Thallium, or $^{99m}$Tc-tetrofosmin). These studies should primarily be reserved for patients in whom the first tier do not reveal metastatic lesions. In the context of advanced DTC, brain MRI imaging is recommended since patients may have brain metastases in the absence of neurological signs or symptoms. Although $^{18}$F-FDG-PET is excellent in identifying non-radioiodine avid metastases in the body (e.g., soft tissue and skeletal metastases), $^{18}$F-FDG-PET is not reliable in the brain due to high glucose metabolism in the brain itself resulting in lower negative predictive value for brain metastasis. Although DTC osseous metastases are typically osteolytic and highly vascularized, bone metastases can occasionally be detected on $^{99m}$Tc MDP bone scintigraphy or $^{18}$F-NaF-PET/CT when the $^{18}$F-FDG-PET/CT is negative. Although the widespread implementation of $^{18}$F-FDG-PET/CT imaging for evaluation of Tg+/scan- patients replaced the routine use of mitochondrial imaging, the different uptake mechanisms of $^{99m}$Tc-sestamibi and $^{18}$F-FDG in the neoplastic cells provides the rationale for selected use of $^{99m}$Tc-sestamibi in difficult patients with suspected metastatic disease not identified by other conventional imaging modalities (e.g., negative $^{131}$I WBS, ultrasound, $^{18}$F-FDG-PET/CT, and CT scan results). (79, 242) The tertiary tier includes somatostatin receptor (SSR) imaging with radiolabeled somatostatin analogs (e.g., $^{99m}$Tc-depreotide, $^{99m}$Tc-EDDA/HYNIC-Tyr3-Octreotide [Tektrotyd], $^{111}$In-octreotide and $^{68}$Ga-DOTATATE/TOC/NOC). A substantial percentage of aggressive histologic variants of DTC (e.g. Hürthle cell, tall cell, insular variants) associated with locoregionally advanced and/or metastatic DTC exhibit cellular expression of SSR, which can be found independently of glucose transporter overexpression (i.e., patients with negative $^{18}$F-FDG-PET/CT imaging). (79) SSR-PET imaging often provides complementary information also in $^{18}$F-FDG+ patients and appears to be especially promising in poorly differentiated and oxyphilic subtypes (i.e. Hürthle cell) metastatic DTC. (243, 244) Peptide Receptor Radionuclide Therapy (PRRT) using radiolabeled somatostatin analogues has shown promise for treatment of $^{131}$I refractory metastatic DTC with demonstrated objective response rate of 20-60% tumor reduction as determined by radiological measurements (RECIST). (245-247) For the future, some promise is shown in individual cases employing $^{68}$Ga-PSMA imaging.

**Step 4: Customize management to the location and number of the metastases**

Once one or multiple metastatic sites are identified, one must decide whether tissue biopsy for histological examination and mutational profile characterization is needed. Focally directed therapy needs to be considered for management of unifocal or oligometastatic disease (e.g. surgical resection, external beam
radiation therapy, alcohol injection, radiofrequency ablation, cryotherapy, embolization, and/or radioisotope embolization). $^{131}$I therapy should be considered if doubt is still present regarding the $^{131}$I refractory status. Systemic and/or combined therapy is recommended for multifocal or widespread metastases.

$^{18}$F-FDG PET/CT imaging for prognosis of metastatic DTC

Approximately 15 - 20% of patients with metastatic DTC and most patients with Hürthle cell thyroid cancer are refractory to radioiodine, and overall survival for these patients ranges between 2.5 - 4.5 years. (60, 222, 248). The prognosis of metastatic DTC is variable, with two distinct phenotypes identified - indolent and aggressive. (249) (250) Patients with iodine-avid metastatic DTC tend to have more favorable prognosis with 10-year survival greater than 90%, while non-iodine avid metastatic DTC has a dire 10-year survival of 10%. (251) On a molecular level, this is largely driven by genetic patterns with specific mutations associated with aggressiveness of thyroid cancer disease. (252) Two studies demonstrated suboptimal predictive value of staging, including the widely used TNM system. (253) (254) Thyroglobulin doubling time (Tg-DT) has been identified as a prognostic factor, with Tg-DT < 1 year portending poor prognosis and Tg-DT > 2 years signifying good prognosis. (255) However, Tg-DT cannot be calculated in the presence of TgAb which invalidate Tg measurements, and it cannot inform regarding the metabolic phenotype and spatial distribution of metastatic lesions. There is a large variability in survival time for patients with metastatic DTC, ranging from 1 year to 30 years. (250) The lack of accurate survival estimates for the individual patient has important implications for treatment decisions, especially regarding the initiation of targeted multikinase therapies. (256, 257) Due to the toxicity profile of these medications, current National Comprehenisve Cancer Network (NCCN) guidelines advocate active surveillance as standard of care in metastatic disease until evidence of symptomatic or clinically progressive disease, as outlined by the RECIST criteria. (258, 259)

$^{18}$F-FDG-PET/CT imaging is particularly useful not only for identification and localization of non-iodine avid metastastases, but has also for predicting the course of disease, as aggressive or indolent. $^{18}$F-FDG-PET/CT has demonstrated prognostic value for survival in metastatic DTC (260), predicting survival disadvantage for patients with positive PET as compared with those with a negative PET scan results. (248, 261) Robbins et al. demonstrated that in patients with metastatic DTC a positive $^{18}$F-FDG-
PET/CT scan result predicted a 7 fold increased risk of mortality as compared with patients who had a negative FDG scan. (248)

$^{18}$F-FDG-PET/CT metabolic parameters can help define the volume and biologic variations of metastatic tumor burden. Specifically, metabolic tumor volume (MTV) and total glycolytic activity (also referred to as total lesion glycolysis, TLG) have been proposed as imaging biomarkers for prognosis in human solid tumors. (262) Robbins et al. demonstrated that total FDG tumor volume, and lesional SUVmax correlate with survival. (248) Wang et al. noted a FDG volume > 125 ml. was associated with worse survival. (260) The metabolic parameters of MTV and TLG obtained with $^{18}$F-FDG-PET/CT imaging have been used as surrogate markers for tumor burden and biologic aggressiveness for prognosis of overall survival (OS) and progression free survival (PFS) in non-iodine avid metastatic DTC. Higher than median MTV and TLG values were associated with worse OS and PFS, with a median OS of only 3.5 years for patients with radioiodine refractory metastatic DTC. (263) This information can be used to guide more rapid implementation of newer therapeutic agents for radioiodine-refractory metastatic DTC and enrollment in clinical trials.

**CONCLUSIONS**

DTC is the most common endocrine malignancy with a rising incidence for the last 30 years. Standard of care for DTC patients is multidisciplinary and involves a risk-stratified approach integrating the information from surgical histopathology, genetic markers, post-operative thyroglobulin levels, and anatomic/functional imaging studies. Early identification of residual nodal and/or distant metastases is particularly relevant for successful $^{131}$I therapy of metastatic disease, since patients who achieve a complete response have considerably higher survival rates than patients with structural incomplete responses. Integration of diagnostic radioiodine scintigraphy in the management algorithm of patients with thyroid cancer should be considered and further multidisciplinary collaborative studies to assess patient-relevant outcome measures (disease-specific survival, recurrence rates and progression free survival) need to be performed.
**Liability Statement**

This guideline summarizes the views of the SNMMI and of the EANM Oncology & Theranostics, Radiopharmacy, Dosimetry, Radiation Protection, Physics, Technologist, and Pediatrics Committees, and of the Romanian, Serbian, British, Italian, Russian, Croatian, Portuguese, Slovak, Macedonian, Estonian, Czech, Polish and Slovenian National Nuclear Medicine collaborating societies. It reflects recommendations for which the EANM cannot be held responsible. The recommendations should be taken into context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions.

**Acknowledgements**

The guidelines were brought to the attention of the relevant SNMMI and EANM Committees and the National Societies of Nuclear Medicine. The comments and suggestions from the EANM Oncology & Theranostics, Radiopharmacy, Dosimetry, Radiation Protection, Physics, Technologist, Pediatrics Committees and the Romanian, Serbian, British, Italian, Russian, Croatian, Portuguese, Slovak, Macedonian, Estonian, Czech, Polish and Slovenian Nuclear Medicine National Societies, as well as the public comments from the SNMMI membership are highly appreciated and have been considered for this Guideline.
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Table 1: Differentiated thyroid cancer: clinical and pathological characteristics

Table 2: Specific dietary instructions for preparatory low-iodine diet

Table 3: Suggested framework for $^{131}$I therapy

Table 4: Response to therapy in DTC patients: dynamic risk stratification criteria

Table 5: Additional considerations before assignment of RAI-Refractory disease status

Table 6: Caveats regarding criteria for Radioiodine Refractory Metastatic DTC

Table 7: Additional Options prior to Radioiodine Refractory Classification

Table 8: Factors considered for management of elevated Tg and negative DxWBS (Tg+/Scan -) patients

Figure 1. Sample Protocol for RAI Theragnostics after Thyroid Hormone Withdrawal (THW)

Figure 2. Sample Protocol for RAI Theragnostics after rhTSH-stimulation (Thyrogen®)

Figure 3. Sample Protocol for RAI Theragnostics with Dosimetry after THW

Figure 4. Sample Protocol for $^{131}$I Theragnostics with Dosimetry after rhTSH-stimulation

Figure 5. Likelihood of Radioiodine Refractory DTC

Abbreviations for Figures 1, 2 & 3:

RAI = radioiodine; L-T4 = Levothyroxine; L-T3 = Liothyronine; Dx RAI Adm. = Diagnostic radioiodine ($^{123}$I, $^{131}$I) activity administration; Dx WBS = Diagnostic radioiodine Whole Body Scan; $^{131}$I Rx = 131-I therapy; PT-WBS = post-therapy $^{131}$I Whole Body Scan; Tg = thyroglobulin; TgAb = thyroglobulin antibodies; THW = stimulation protocol by thyroid hormone withdrawal; rhTSH = recombinant human TSH; LID = 2 weeks of low-iodine diet; TSH = Thyroid Stimulating Hormone; F-T4 = Free Thyroxine; Tg = Thyroglobulin
Table 1. Differentiated thyroid cancer: clinical and pathological characteristics. (5)

<table>
<thead>
<tr>
<th>Histological subtypes</th>
<th>Morphology</th>
<th>Molecular markers</th>
<th>Pattern of Spread</th>
<th>RAI avidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary thyroid cancer (PTC)</td>
<td>Classical papillae Clear nuclei</td>
<td>BRAF V600E, RET/PTC fus</td>
<td>Lymph nodes</td>
<td>+++</td>
</tr>
<tr>
<td>PTC-Follicular variant (fvPTC)</td>
<td>Follicular structures Clear nuclei</td>
<td>BRAF K601E, RAS, PAX8/PPARγ</td>
<td>Lymph nodes</td>
<td>++++</td>
</tr>
<tr>
<td>PTC-Aggressive variants*</td>
<td>Specific cell features and structural changes</td>
<td>BRAF V600E, 1q amp, TERT promoter</td>
<td>Lymph nodes Lung</td>
<td>+++</td>
</tr>
<tr>
<td>Follicular thyroid cancer (FTC)</td>
<td>Capsular invasion (MI) Vascular invasion (WI) Extrathyroidal invasion (WI)</td>
<td>RAS, PAX8/PPARγ, PTEN, TSHR, TERT promoter</td>
<td>Lung Bone</td>
<td>++++</td>
</tr>
<tr>
<td>Hurthle cell thyroid carcinoma</td>
<td>Hurthle cells</td>
<td>RAS, PAX8/PPARγ, PTEN, TSHR, chromosomal loss, mitochondrial DNA mutations, TERT promoter</td>
<td>Lung Bone</td>
<td>++</td>
</tr>
<tr>
<td>Poorly differentiated thyroid cancer (PDTC)</td>
<td>Invasion Mitoses &gt;3 Necrosis Convoluted nuclei</td>
<td>RAS, TERT promoter, TP53, PIK3CA, PTEN, CTNNB1, AKT1, EIF1AX, ALK fus</td>
<td>Lymph nodes Lung Bone</td>
<td>+/-</td>
</tr>
<tr>
<td>Anaplastic thyroid cancer</td>
<td>Undifferentiated cells with immunoistochemical or ultrastructural features of epithelial origin but of morphological and immunophenotypic markers of thyroid origin</td>
<td>TP53, TERT promoter, PI3K/AKT/mTOR, SWI/SNF subunits, RAS, EIF1AX, BRAF</td>
<td>Local invasion Lung Bone Lymph nodes</td>
<td>-</td>
</tr>
</tbody>
</table>

Legend: MI, minimally invasive; WI, widely invasive; fus, fusion; (*) tall, columnar, solid, hobnail variants.
Table 2: Specific dietary instructions for preparatory low-iodine diet

<table>
<thead>
<tr>
<th></th>
<th>ALLOWED</th>
<th>RESTRICTED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baked goods, Pasta</strong></td>
<td>Flour, oatmeal, wheat, macaroni, noodles, pancakes, spaghetti, homemade bread prepared with non-iodized salt</td>
<td>Cereals, rice, granola, popcorn; industrialized biscuits, breads, crackers</td>
</tr>
<tr>
<td><strong>Meat, Poultry, Eggs</strong></td>
<td>Beef, lamb, chicken, turkey, pork, veal; eggs-(max 2 eggs per week)</td>
<td>All seafood (fish, shrimp, oysters, clams, etc); processed, cured, smoked or breaded meats</td>
</tr>
<tr>
<td><strong>Condiments</strong></td>
<td>Salt-free margarine, vegetable oil, mayonnaise, sugar, jelly, honey</td>
<td>Iodized salt, pickles, white sauce, meat sauces, creamy sauces, soy sauces, agar-agar, unsalted nuts, vinegar or alginate additives, red colorants</td>
</tr>
<tr>
<td><strong>Fruits, Juices</strong></td>
<td>All raw fruits and homemade natural juices</td>
<td>Fruit cocktails, canned fruits, dried fruits</td>
</tr>
<tr>
<td><strong>Beverages</strong></td>
<td>Water, tea, coffee, wine, alcoholic drinks</td>
<td>Milk and all derivatives (yogurt, ice cream, cheese), soy beverages</td>
</tr>
<tr>
<td><strong>Desserts</strong></td>
<td>Homemade cookies, homemade fruit pies, homemade cakes (prepared with non-iodized salt)</td>
<td>Chocolate, pudding, gelatin, ice cream, candies, industrialized desserts, foods with red colorants, molasses</td>
</tr>
<tr>
<td><strong>Vegetables</strong></td>
<td>Asparagus, beets, broccoli, cabbage, celery, carrots, cauliflower, corn, cucumber, lettuce, mushrooms, onions, peas, potatoes without peel, spinach, sweet potatoes (baked), tomatoes (fresh), zucchini</td>
<td>All canned vegetables, potatoes with peel, french fries, candied sweet potatoes, onion rings, beans</td>
</tr>
<tr>
<td><strong>Combination Dishes</strong></td>
<td>Homemade dishes prepared with allowed ingredients</td>
<td>Pizza, lasagna, macaroni and cheese, industrialized foods and foods with conservants</td>
</tr>
</tbody>
</table>

All dishes must be prepared with non-iodized salt. Avoid eating in restaurants.
Table 3: Suggested framework for $^{131}$I therapy

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Prescribed $^{131}$I activity</th>
<th>Clinical/Pathological Context</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk-adapted $^{131}$I therapy</td>
<td>1.11-1.85 GBq (30-50 mCi) $^{131}$I *</td>
<td>Remnant Ablation</td>
</tr>
<tr>
<td>Risk-adapted $^{131}$I therapy</td>
<td>1.85-3.7 GBq (50-100 mCi) $^{131}$I ¥</td>
<td>Adjuvant Treatment</td>
</tr>
<tr>
<td>Risk-adapted $^{131}$I therapy</td>
<td>3.7-5.6 GBq (100-150 mCi) $^{131}$I</td>
<td>Treatment of small volume local-regional disease</td>
</tr>
<tr>
<td>Risk-adapted $^{131}$I therapy</td>
<td>5.6-7.4 GBq (150-200 mCi) $^{131}$I</td>
<td>Treatment of advanced local-regional disease and/or small volume distant metastatic disease</td>
</tr>
<tr>
<td>Whole body/blood dosimetry</td>
<td>$\geq$ 7.4 GBq ($\geq$ 200 mCi) $^{131}$I, maximum tolerable safe $^{131}$I activity</td>
<td>Treatment of diffuse distant metastatic disease</td>
</tr>
</tbody>
</table>

* FDA approved the use of rhTSH in combination with 100 mCi $^{131}$I for remnant ablation in December, 2007. (146) (147)

¥ Some committee members recommend up to 5.6 GBq (150 mCi) without extant data regarding the effectiveness and toxicity profile of 1.85 GBq (100 mCi) vs. 5.6 GBq (150 mCi) for adjuvant treatment.

Current guidelines advise that the frequency and severity of side effects are activity-dependent, specifically increased xerostomia risk for $> 3.7$GBq (100 mCi), and sialadenitis risk for $> 5.6$ GBq (150 mCi). (148)
Table 4. Response to therapy in DTC patients: dynamic risk stratification criteria [modified from (6)]

<table>
<thead>
<tr>
<th>Excellent response:</th>
<th>no clinical, biochemical or structural evidence of disease: negative imaging and either suppressed Tg &lt;0.2 ng/mL or stimulated Tg &lt;1 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical incomplete response:</td>
<td>abnormal Tg (i.e. suppressed Tg &gt;1 ng/mL or stimulated Tg &gt;10 ng/mL or rising anti-Tg antibody levels in the absence of localizable disease (i.e. negative imaging))</td>
</tr>
<tr>
<td>Structural incomplete response:</td>
<td>persistent or newly identified loco-regional or distant metastases (any Tg value)</td>
</tr>
<tr>
<td>Indeterminate response:</td>
<td>nonspecific biochemical (i.e. suppressed Tg 0.2-1 ng/mL or stimulated Tg 1-10 ng/mL or stable/declining anti-Tg antibody levels) or structural findings that cannot be confidently classified as either benign or malignant.</td>
</tr>
</tbody>
</table>

Table 5. Additional considerations before assignment of radioiodine refractory disease status (225)

- Appropriate preparation of the patient for diagnostic and/or post-therapy RAI scan (39, 241)
- Results of the diagnostic scan.
- Results the post-therapy scan.
- The response to the last $^{131}$I therapy
- The criteria for progression.
- The time to progression.
- The activity of $^{131}$I administered for the last $^{131}$I therapy.
- Total accumulative activity of $^{131}$I administered.
- The objectives of $^{131}$I therapy, (e.g., cure, progression free survival, overall survival, palliation).
- Location and number of metastases. They may be radioiodine avid, but perhaps focal direct therapy (e.g., surgery, XRT, cryotherapy, etc.) may be more effective, warranted or desired.
- Type, frequency, and severity of side effects of $^{131}$I therapy
- Patient’s desires (e.g. patient is a “minimalist” or “maximalist”) (264)
Table 6. Caveats regarding criteria for radioiodine refractory metastatic DTC [adapted from (225)]

- The observation that a patient does not demonstrate radioiodine uptake on a diagnostic scan or post-therapy scan does not necessarily mean that patient’s metastatic disease is radioiodine refractory.
- The observation that a patient does demonstrate radioiodine uptake on a diagnostic scan or post-therapy scan does not necessarily mean that patient’s metastatic disease is responsive to an $^{131}$I therapy.
- As the total accumulative activity of administered $^{131}$I increases, the likelihood of a response to a subsequent $^{131}$I therapy decreases. However, no maximum accumulated threshold of administered $^{131}$I activity should designate that a patient’s metastatic disease is radioiodine refractory.
- One metastatic lesion that is classified as radioiodine refractory does not necessarily mean the patient is now radioiodine refractory. Combination therapy of direct focal therapy (e.g., surgery, external beam radiotherapy, radiofrequency ablation, cryotherapy, embolization, radioisotope embolization) or with targeted therapy (e.g., tyrosine kinase inhibitors, BRAF inhibitors, etc.) in combination with $^{131}$I therapy may benefit the patient.
- Progression, in and of itself, is not a criterion that an $^{131}$I therapy has “failed” and that a patient’s metastatic disease is “radioiodine refractory.” Additional factors such as duration of progression free survival and administered activity of $^{131}$I are important.

Table 7. Additional Options prior to radioiodine refractory classification

- Consider a “blind” $^{131}$I therapy (see text)
- Refer the patient to a site that performs dosimetry
- Refer the patient to a site that routinely manages metastatic DTC
- Consider exploring the patient’s eligibility for participating in a study that offers “re-sensitizing” or “redifferentiating” agents to see if radioiodine uptake can be re-established or increased for a potential $^{131}$I therapy
Table 8. Factors considered for management of elevated Tg and negative DxWBS (Tg+/Scan -) patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment objectives</td>
<td>(i.e., cure, progression free survival, palliation)</td>
</tr>
<tr>
<td>The time interval since the last $^{131}$ I treatment</td>
<td></td>
</tr>
<tr>
<td>The amount of $^{131}$ I activity administered for the most recent</td>
<td></td>
</tr>
<tr>
<td>The response to the most recent $^{131}$ I treatment (if there has</td>
<td></td>
</tr>
<tr>
<td>Total cumulative $^{131}$ I therapeutic activity</td>
<td></td>
</tr>
<tr>
<td>Frequency and severity of side effects of prior $^{131}$ I therapies,</td>
<td></td>
</tr>
<tr>
<td>Is the patient a minimalist or maximalist regarding benefit vs risk of</td>
<td></td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
</tr>
<tr>
<td>Capabilities of the treating facility</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Sample Protocol for $^{131}$I Theragnostics after Thyroid Hormone Withdrawal (THW)

Figure 2. Sample Protocol for $^{131}$I Theragnostics after rhTSH-stimulation

Figure 3. Sample Protocol for $^{131}$I Theragnostics with Dosimetry after Thyroid Hormone Withdrawal

Figure 4. Sample Protocol for $^{131}$I Theragnostics with Dosimetry after rhTSH-stimulation

Figure 5. Likelihood of Radioiodine Refractory DTC