One Hundred Years of Lung Cancer

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A hundred years ago, lung cancer was a reportable disease, and it is now the commonest cause of death from cancer in both men and women in the developed world, and before long, will reach that level in the developing world as well. The disease has no particular symptoms or signs for its detection at an early stage. Most patients therefore present with advanced stage IIIIB or IV disease. Screening tests began in the 1950s with annual chest x-ray films and sputum cytology but they resulted in no improvement in overall mortality compared with control subjects. The same question is now being asked of spiral low-dose computed tomographic scanning. There have been big refinements in the staging classification of lung cancer and advances in stage identification using minimally invasive technology. Postmortality has declined from the early days of the 1950s but 5-year cure rates have only barely improved. The addition of chemotherapy to radical radiotherapy, together with novel radiotherapy techniques, is gradually improving the outcome for locally advanced, inoperable non–small cell lung cancer. Chemotherapy offers modest survival improvement for patients with non–small cell lung cancer, the modern agents being better tolerated resulting in an improved quality of life. The management of small cell lung cancer, which appeared so promising at the beginning of the 1970s, has hit a plateau with very little advance in outcome over the last 15 years. The most important and cost-effective management for lung cancer is smoking cessation, but for those with the disease, novel agents and treatment approaches are urgently needed.

Keywords: lung cancer; one hundred years; staging; treatment

One hundred years ago, lung cancer was a reportable condition and now it accounts for more deaths worldwide from cancer than any other malignant disease. In 1912, Adler published a book entitled Primary Malignant Growth of the Lungs and Bronchi, where he reported all cases of lung cancer in the published literature worldwide. He could verify only 374 cases (1). Smoking was popularized during the First World War, when General John J. “Black Jack” Pershing reportedly stated, “I answer tobacco as much as bullets” (2). Still, esteemed surgeon Alton Ochsner recalled that as a student at Washington University in 1910, he was asked to witness an autopsy of a patient with lung cancer, having been told lung cancer was so rare that he may never see another case. It was 17 years before he saw his next case at Charity Hospital in New Orleans. Within the next 6 months eight more cases were seen at that hospital (all in men who smoked heavily) and this began what he called an epidemic (3). Today, in the United States, the combined annual number of deaths from breast, colon, and prostate cancer would not equal the death toll from lung cancer, and last year more than 150,000 patients died of this disease. It represents the most preventable respiratory disease worldwide and, while its incidence is decreasing in the developed world, an epidemic of untold proportions is unfolding in the developing countries. Advances in imaging, diagnosis, staging, and treatment have come relatively recently, but despite our best efforts, the 5-year survival for this disease remains a dismal 16% in the United States and 5% in the United Kingdom. This short review hopes to highlight areas and times of progress with this disease.

EPIDEMIOLOGY

There have been several historic breakthroughs over the century but none more important than Sir Richard Doll and Austin Hill’s landmark article, published in 1950 in the British Medical Journal, which confirmed suspicions that lung cancer was associated with cigarette smoking (4). (The smoking history enquiry was added only because the final page was half empty!) The importance of this article cannot be underestimated as smoking rates were at their peak in the United States and Europe after the Second World War, physicians could be seen advocating smoking in tobacco advertisements, and the claims by the tobacco industry that smoking was safe went completely unchallenged. The second landmark publication was the U.S. Surgeon General’s report in 1964, in which he stated that smoking was harmful to health and efforts should be made not to take up the habit or to quit (5). Smoking rates have declined since that report, with a proportional decrease in lung cancer rates lagging some 20 years behind. While lung cancer rates were less than 5 per 100,000 at the start of the 20th century in the United States (6, 7), by 1998, the age-adjusted death rate per 100,000 population for men had reached 77.2 in Belgium and 75.5 in Scotland, with the 10 highest rates all in European countries. The 10 lowest rates for men were found primarily in South America and Asia.

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estimated that nearly 800,000 Chinese men would die of lung cancer in 1998 (8). Others have predicted that China, where one-third of the world’s smokers reside, will have millions of lung cancer deaths annually by the middle of the 21st century (12). The average number of cigarettes smoked by every adult male in China is 11/day, with 67% of the male population smoking, equivalent to the highest rates ever seen in the United States. The consumption of cigarettes in China may surpass that of all of the developed countries combined (8, 13). Needless to say, while educational efforts continue to pay dividends in the developed world, organizations such as the World Health Organization and all the respiratory societies have an obligation to educate those in developing nations about the detrimental effects of tobacco abuse in the same way that efforts at the eradication of tuberculosis have occurred. For the sake of completeness, one should mention the other causes or associations with the development of lung cancer, which include radon, second-hand smoke, and asbestos exposure, among others.

SCREENING

There have been two major efforts to screen for lung cancer over the last century: the first was based on chest radiographs in the 1970s and 1980s and the second has used low-dose computed tomography (CT), and is ongoing today. The results of randomized trials using the chest radiograph failed to show a reduction in lung cancer mortality in the screened group (14–16). These studies have been criticized for being underpowered and having high contamination rates in the control groups. Because of the deficiencies in these trials, a large trial sponsored by the National Cancer Institute, the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial, has been underway for about 10 years. The lung arm randomized persons to screening with chest radiograph versus no screen in smokers. It is powered to detect a 10% reduction in mortality due to lung cancer but the final results will not be available for several years.

A resurgence in interest for screening occurred at the turn of this century with the understanding that CT is much more sensitive for detecting pulmonary nodules than the standard chest radiograph. There have been several uncontrolled trials using low-dose spiral CT (16–22). These have shown that spiral CT detects more lung cancers than does chest radiograph, but also a high prevalence of noncalcified nodules. The low-dose CT trials have shown a stage shift, with a higher proportion of cancers than expected detected at an earlier, presumably more curable, stage. However, it is not possible to determine whether this is due to lead time, length time, or overdiagnosis bias. Furthermore, it is unclear whether the evaluation of patients with noncalcified nodules will lead to an unacceptably high rate of morbidity or mortality in the screened group without cancer. Thus, a randomized controlled trial is needed, with the primary end point being a reduction in mortality from non–small cell lung cancer (NSCLC). The National Lung Cancer Screening Trial will randomize 50,000 high-risk participants to screening with CT or chest radiograph. Subjects will be screened yearly for 3 years and followed up for another 5 years. The trial completed accrual in 2004, but final results may not be available for at least 5 years.

STAGING

The staging of lung cancer has undergone significant evolution over the last century. Today, appropriate staging is critical as the treatment options and prognosis are vastly different for each stage. The most significant dividing line is between those patients who are candidates for surgical resection and those who are inoperable, but will benefit from chemotherapy or radiation therapy or both. The basis for staging NSCLC is the TNM (tumor, nodal involvement, distant metastasis) system (23, 24). The majority of lung cancers are initially detected by plain chest radiograph. Up until the 1970s, chest radiograph was the only tool available for staging lung cancer. Unfortunately, plain radiograph is both insensitive and nonspecific in diagnosing the extent of disease within the chest.

CT of the chest was introduced in the late 1970s. Numerous evaluations of CT were performed that compared clinical staging by CT with the “gold standard” of mediastinoscopy or surgery. These studies demonstrated that regardless of threshold size, CT findings in isolation could not be considered conclusive evidence that lymph nodes were malignant. In other words, in all studies there is an unacceptably high rate of “false positives” detected by CT scan (25, 26). Still, CT remains the most widely used imaging test to stage patients with lung cancer. The test is useful in defining the extent of the tumor; whether there is involvement of vascular structures, mediastinum, or chest wall; and to assess the size of the mediastinal lymph nodes. Unfortunately, about 40% of all nodes deemed malignant by CT criteria are actually benign depending on the patient population, and specificity can be affected by clinical factors such as the presence of postobstructive pneumonitis (27).

Another modality for staging lung cancer is positron emission tomography (PET), which is based on the biologic activity of neoplastic cells. Lung cancer cells demonstrate increased cellular uptake of glucose and a higher rate of glycolysis when compared with normal cells (28). The radiolabeled glucose analog 2-[18F]fluoro-2-deoxy-D-glucose (FDG) accumulates in cells that have high glucose utilization and can then be identified with a PET camera. A number of studies have reported on the utility of CT and FDG-PET scanning in the assessment of patients with lung cancer (25, 26). Pooled data evaluating the accuracy of CT scanning for staging the mediastinum were identified, combining 4,793 evaluable patients. The pooled sensitivity of CT scanning for staging the mediastinum was 0.60 (95% CI, 0.51–0.68) and the pooled specificity was 0.81 (95% CI, 0.74–0.86). The pooled sensitivity of PET was 0.85 (95% CI, 0.79–0.89) and the pooled specificity was 0.88 (95% CI, 0.82–0.92). Thus, it appears that PET has both higher sensitivity and specificity for evaluation of mediastinal lymph nodes than does CT scanning (25).

One randomized trial revealed that futile thoracotomies could be avoided in about 20% of patients previously believed to be resectable (29). Although PET has a much higher overall accuracy than CT for detecting both intra- and extrathoracic disease, both false positives and negatives are reported. Thus, tissue confirmation of abnormal findings discovered on either modality is the rule in most cases. Improvements in technology have increased our use of bronchoscopy with transbronchial needle aspirate, endoscopic ultrasonography, mediastinoscopy, thoracoscopy, and transthoracic needle biopsy to allow for minimally invasive tissue procurement and more accurate staging (30). Although these minimally invasive techniques have now become commonplace, mediastinoscopy remains the gold standard for tissue procurement, with its extremely high sensitivity and specificity coupled with low morbidity.

TREATMENT

The principles of treatment have changed little over the last 50 years, and remain surgery, radiotherapy or chemotherapy, or a combination of one or all of these. In the first half of the 20th century, there was no effective treatment for lung cancer. During the last 50 years, surgery has become safer, and remains the
As surgery became more feasible, it became clear that the principal modality to offer a chance for cure, and techniques, including preoperative staging, have become considerably refined. The administration of radiotherapy has also become more sophisticated, with higher dose treatments increasingly feasible, better field planning, and more focused targeting. Chemotherapy has also improved, with virtually none of the agents used in the 1950s–1970s being given today and with appreciation of optimal scheduling, duration of therapy, and attention to side effects and quality of life. Despite this, the 1- and 5-year survival rates for all cases of lung cancer in the United Kingdom over the last 30 years. Light bars = male, 1 year; dark bars = female, 1 year; medium dark bars = male, 5 years; medium light bars = females, 5 years.

The first deliberate attempt at pulmonary resection was in 1821, when an American, Milton Anthony, removed “one or two pounds of pulmonary tissue” along with two portions of ribs. The patient survived the operation only to die 1 year later. The first successful pneumonectomy for lung cancer was in 1933; the patient went on to practice medicine and it dramatically showed the world that this was a curable disease (32).

As surgery became more feasible, it became clear that the majority of patients were technically unsuitable for resection because of obvious dissemination of disease, but also that many patients, although technically operable, still represented too much risk. Most of the latter causes were due to concomitant disease, in particular heart disease, but in others the prospect of a pneumonectomy was too great for their preoperative lung function. By 1970, it was shown that adverse prognostic factors included weight loss of more than 10 pounds, physical evidence of cancer, pneumonectomy, obstruction of a bronchus, blood vessel invasion, lymphatic invasion, lobar node involvement, and hilar or mediastinal node involvement. Favorable factors included age under 60 years, operation on the right, and tumor confined to the lung (33). Surgeons were also engaging in controversy concerning whether to operate on those aged more than 70 years (nearly half of today’s lung cancer population in the Western world) (34). Efforts in the 1960s and 1970s showed mortality ranging between 3 and 17% within 30 days of surgery, but already emphasis was on careful selection and lung-sparing procedures whenever possible (35–37).

The most important development in surgery was staging, which was first hinted as being of relevance in 1876 when Parrot pointed out that changes in the hilar lymph nodes frequently reflect diseases in the lungs. Daniels demonstrated in 1949 that the lymph nodes in the scalene fat pads often showed the same pathology as was suspected in the chest and that a biopsy of these nodes could be of diagnostic value. Harken and colleagues, dissatisfied at the poor yield of this method, were the first to show that exploration of the upper neck and mediastinum was feasible. However, this was at first only a unilateral approach, which was a distinct disadvantage, especially as it became apparent that with lung cancer contralateral spread in the superior mediastinum occurred not uncommonly. In 1959, Carlens devised mediastinoscopy as it is known today (38). The accessibility of some of the central thoracic structures led to the development of accurate subclassification of tumor extent and the TNM classification was applied to this disease in 1974 (Figure 2) (39).

For NSCLC, resection remains the first modality to consider. As patients are increasingly elderly, attempts to resect tumors in the elderly in particular have led to lung-conserving surgery, especially wedge resections and concomitant tumor resection as part of lung volume reduction surgery in advanced chronic obstructive pulmonary disease. Wedge resection was already being performed in the early 1970s (36, 40), often in patients who had a second cancer in the contralateral lung after initial resection. The 5-year survival rates were about 55%, although the early death rate was high among those who had undergone a previous contralateral resection. Although wedge resection does appear an attractive alternative, particularly for those with compromised lung function, both retrospective and prospective studies show a higher recurrence rate and a trend toward worse survival (41). This approach, although not the treatment of choice, still offers these high-risk patients a chance for cure.

The ready use of CT scanning will allow recognition of small tumors and this will make less invasive surgery feasible. Video-assisted thoracoscopic surgery can be used for wedge resection and even lobectomy for smaller tumors, although the ability of this technique to provide formal intrathoracic nodal sampling—that is, full staging—remains controversial. However, the technique is associated with less preoperative morbidity, better pain control, and shorter in-hospital stay.

The 5-year survival for pneumonectomy remains at about
40% because of the more advanced nature of the resected disease (42). It also carries a higher perioperative mortality than lobectomy (8–10 vs. 2–4%) and is particularly difficult for elderly patients.

Efforts to improve the cure rates for those undergoing resection after modern staging include neo- and adjuvant chemotherapy, some trials also including pre- or postoperative radiotherapy. It is surprising that the results of only three randomized controlled trials of neoadjuvant chemotherapy have been published. Two were small but also significantly in favor of the neoadjuvant arm (43, 44), but a much bigger trial of 325 patients failed to confirm the advantage (45). Thus only about 450 patients have been subjected to careful randomized studies concerning this important question. The chemotherapy used in these studies was not “modern” and newer regimens are now being tested in randomized controlled trials.

There has been more success in assessing the role of adjuvant chemotherapy. It seemed to confer an approximately 5% advantage over surgery alone in a large meta-analysis of all randomized controlled trials asking this question in 1995 (46). Since then, large studies have been both positive (47) and negative (48, 49), although two recent, as yet unpublished, trials from the United States and Canada (50, 51) are strongly positive for early-stage resected cases. Patients will be asked increasingly to consider postoperative chemotherapy after a curative resection, as a further 5% survival advantage in a common disease is important. However, as yet, there is no consensus recommendation for this additional treatment. Nevertheless, this improvement in longer term survival is as good as or better than that seen with adjuvant therapy in other solid tumors.

RADIOThERAPY

As a curative modality, radiotherapy has been disappointing. In locally advanced disease it controls tumor growth and reduces recurrence rates, but despite trials with escalating doses up to 80 Gy, it has a 5-year survival rate of 7 to 10% (52, 53). The standard radical dose in NSCLC remains at about 60 Gy, which is a compromise between an adequate dose and minimizing lung and esophageal toxicity. Novel ways of dose intensification have been explored, the most promising being hyperfractionation. The British Medical Research Council study of continuous hyperfractionated accelerated radiotherapy (CHART) with fractions of 1.5 Gy administered at 8-hour intervals to a total of 54 Gy versus conventional daily treatment showed a striking advantage for CHART, especially for squamous cell tumors, with 30 versus 20% survival at 2 years (54). Despite what seemed a major advance in the administration of radiotherapy, the daily approach foudered with the impracticality of managing to continue over the weekend. Also, patients had to be “grouped” for cost reasons. CHART is now being superceded by CHARTWEL, that is, with weekend leave, which may be as effective.

The combination of chemotherapy and radiotherapy has provided better median and longer term survival than radiotherapy alone. Not all studies comparing the two treatments have shown an advantage for the combined approach. The NSCLC Collaborative Group meta-analysis of 1995 found a benefit of 4% at 2 years and 2% at 5 years (46). Several subsequent studies have shown similar advantages for the combined modality (55), but it is still not clear what the sequencing of the treatments should be. There is a suggestion that concurrent chemoradiation is superior to sequential chemotherapy followed by irradiation. The only published randomized controlled trial to date showed a 4-month median survival advantage for concurrent treatment (16 vs. 12 months) (56). The future for radiotherapy appears to be with careful field planning, using CT and three-dimensional planning to more precisely define the limits of the tumor and to allow a higher dose to be given safely in a focused manner. Finally, as radical therapy relies on the tumor being confined to the irradiated site, PET will have a significant role in pretreatment staging.

Radiotherapy has proven most successful in palliating lung cancer symptoms in up to 80% of instances, including bone pain, hemoptysis, cough, superior vena caval syndrome, and, to a lesser extent, cerebral metastases. Single fractions of 8 Gy or two fractions of 17 Gy are as effective as longer bigger treatments, making palliation feasible for outpatient visits (57, 58).

Radiotherapy was considered the treatment of choice for small cell lung cancer (SCLC) in the 1960s. The British Medical Research Council conducted a trial comparing surgery with radiotherapy with rather equivalent results, 3 and 7% survival at 4 years, respectively. In their 10-year follow-up report, they confirmed that “a patient with oat cell carcinoma on bronchoscopic biopsy should submit to radiotherapy rather than surgery” (59). Subsequent studies of the natural history of this cell type revealed its enormous propensity to be disseminated at presentation, and rendered both these modalities virtually redundant as primary treatments.

In SCLC, with the emergence of chemotherapy as a systemic treatment radiotherapy was examined as a means to enhance local control of the primary tumor site, particularly after a partial or complete response to chemotherapy. The advantage for the addition of radiotherapy after chemotherapy was confirmed in meta-analyses after several randomized controlled trials had produced mixed messages. One was based on 1,911 published cases in trials and looked at 2-year survival, local control, and toxicity (60). The other included 2,140 patients and looked at the 3-year survival and prognostic factors (61). Both showed modest improvements in survival rates in those given thoracic radiotherapy. At 3 years, 9% of patients who received chemotherapy alone and 14% of those who received combined modality treatment were alive, with a 14% reduction in the risk of death for the combined approach. Radiotherapy thus became the standard for responding patients; however, the precise timing of the radiotherapy has been the subject of further trials. These have examined giving it early (within 9 weeks of starting chemotherapy) or late, that is, at the end of chemotherapy, or with the last course of treatment. Some studies found a survival advantage for early radiotherapy (62, 63) whereas other, similar studies did not (64, 65). Although the doses and fractionation schedules varied between these studies, the message appears to be that hyperfractionated radiotherapy given early may be more effective than single daily fractionation schedules, given early or late (66). However, the most important factor would seem to be to deliver the chemotherapy at optimal intensity. Failure to deliver chemotherapy adequately, especially if given concurrently with radiotherapy, may limit any potential benefit.

CHEMOTHERAPY

The natural history of advanced NSCLC is particularly poor, with a median survival of 4 to 6 months. Early trials with chemotherapy showed response rates of 10 to 15%, disappointing compared with more than 50% for SCLC. The gain over best supportive care was about 6 weeks, with a 10% improvement in survival at 1 year (46). This advantage was seen only for cisplatin-containing regimens, and the early choices of long-acting alkylating agents plus, for example, cyclophosphamide, vinblastine, or methotrexate were associated with worse results than best supportive care alone. Over the last 10 years, newer agents have emerged that have provided slightly better median and 1-year survival, 7–10 months, with 35 to 40% alive at 1 year (67, 68). However,
the main advantage of modern chemotherapy with carboplatin, plus vincristine, gemcitabine, or a taxane has been easier administration on an outpatient basis; fewer side effects, such as nausea, vomiting, and hair loss; and an improvement in quality of life, which had been overshadowed and lost by the side effects of the chemotherapy itself (69). The results from treatment trials in advanced NSCLC apply to a minority of patients with the disease, as trials tend to be conducted in patients with better performance status, younger individuals, and those attending interested treatment centers. Despite lung cancer being increasingly a disease of the elderly, less than 20% of patients over 70 years of age enter treatment trials. Also, trials have been limited in the main to those with good performance status (ECOG 0-1), whereas many present with performance status level 2 or 3. Much more needs to be done in future to include the elderly and to devise acceptable treatment regimens for poorer performance status patients. There is good evidence that, fit, good-performance-status elderly patients respond just as well as younger individuals (70). Similarly, although poorer performance status patients are unlikely to live as long as their fitter counterparts, they do respond to chemotherapy with an improvement in quality of life for a time.

With these problems in mind, it is timely that a new approach to treatment is emerging with targeted therapy. Mutations in the epidermal growth factor receptor (EGFR) have been identified in NSCLC, and overexpression of EGFR and its ligands has made it an attractive target for various antitumor strategies. Aberrant signaling from the EGFR is known to be important in the development and progression of NSCLC. Two oral inhibitors of EGFR, gefitinib and erlotinib, are small molecule agents that selectively inhibit the intracellular tyrosine kinase activity of the EGFR. Both have demonstrated antitumor activity in patients with advanced NSCLC who have relapsed after treatment with conventional chemotherapy regimens, with a low toxicity profile. Two randomized phase II studies of gefitinib have examined differences between two doses of the drug in relapsed disease (71, 72). These have shown tumor responses and improvement in symptom control. A placebo-controlled trial of erlotinib, also in relapsed, advanced NSCLC, has shown a survival advantage for the active arm, again with better quality of life (73). Although EGFR expression is common in NSCLC, responses to these agents are few, and seem particularly associated with nonsmokers, women, and patients with bronchoalveolar cell carcinomas. Furthermore, a report has identified specific mutant versions of EGFR in NSCLC cells in biopsies of patients who respond to gefitinib (74). To date, these mutations have been found only in NSCLC and seem to be present in about 10% of biopsy samples. These mutations may identify those who will respond, but the number of responders seems to exceed the percentage of those with the mutation.

Other EGFR-tyrosine kinase inhibitors are under investigation, including the monoclonal antibody cetuximab, which has been approved for the treatment of colorectal cancer. The antangiogenic vascular endothelial growth factor monoclonal antibody bevacizumab has also been allowed for the treatment of colorectal cancer. Thalidomide, another antiangiogenic substance, is in clinical trials with chemotherapy in both NSCLC and SCLC.

Small cell lung cancer remains the most frustrating cancer to treat and little progress has occurred. In randomized trials in the 1970s, there was some optimism concerning SCLC treatment as several active single chemotherapy agents were discovered, and these became more active in combinations of two or three drugs. Objective responses were seen in 80 to 90% of those treated, and the median survival rose rapidly from 5 months untreated to 18 to 20 months for those with limited disease, and from a matter of weeks untreated to 6 to 9 months for those with extensive disease. The best survivals were seen in patients with good performance status, and normal values for serum sodium, alkaline phosphatase, and urea (75). Sadly, there has been little further improvement. Better tolerated chemotherapy regimens have been introduced, for example, etoposide and carboplatin. Radiotherapy to the mediastinum in responding patients adds to long-term survival, and prophylactic whole brain radiotherapy prevents the high morbidity of cerebral relapse. Many attempts to intensify chemotherapy, either initially, or late, or with bone marrow or granulocyte-macrophage colony-stimulating factor support have all failed to improve the prognosis. Patients continue to benefit from treatment because of the high rates of response and a significant improvement in quality of life for these very symptomatic sufferers. However, as with NSCLC, treatment with second-line chemotherapy at relapse has a disappointing effect with few responses and short progression-free intervals. It seems that most attention today is on the less responsive NSCLC and we have moved away from SCLC despite its much greater potential for response to therapy.

In summary, lung cancer was a virtually nonexistent disease 100 years ago. Arguably, the most significant advance in this disease has been the recognition that smoking is the causal agent. There have been major technical advances in imaging, surgical technique, and the use of chemotherapy and radiotherapy to treat this disease. Unfortunately, these advances have brought only small improvements in survival. Nonetheless, those in cancer research remain hopeful that improvements in survival will come in the decades ahead. No diagnostic or treatment modality will have nearly the effect on mortality as the elimination of tobacco products from the marketplace. As Johnston wrote, “Hippocrates never heard of it” (76). It would be nice if, at the bicentennial review of diseases of the chest, lung cancer could be relegated to a historical footnote.

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References


