REVIEW

Carcinoma of the bronchus 60 years later

G A Silvestri, S G Spiro

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The subject of malignant disease of the lung, particularly bronchogenic carcinoma, appears to be a suitable one for such an occasion as this for many reasons. It is a condition of considerable importance owing to its increasing incidence; it clearly illustrates the advance in diagnosis and treatment in chest disease obtained during the last 20 years. It affords, in all its various aspects, opportunities to all sections of this association for study, and, lastly, it is a subject which has always been of considerable interest to me personally (excerpt from A Tudor Edwards).[1]

Above the readers of today's *Thorax* will find the introduction to the first article ever published in this journal. The article was written by A Tudor Edwards and is based upon his presidential address to the association for the study of diseases of the chest on 27 July 1945. Despite the fact that this address was given 60 years ago and about 2 months after VE day celebrations signalling the end of World War II, it could just as easily have been given in the year 2006. For certain, lung cancer is a condition of considerable importance in the world today. It is the leading cause of preventable cancer death worldwide. Clearly, there have been advances in the diagnosis, staging, and treatment over the past 60 years. As asserted by Tudor Edwards 60 years ago, lung cancer lends itself to a multidisciplinary approach with respiratory physicians, thoracic surgeons, oncologists, and radiotherapists working jointly to study the disease while providing comprehensive cancer care.

Throughout the remainder of this article we will endeavour to provide an update in lung cancer while paying particular attention to how far we have come from then until now. Where possible we will use excerpts from the original article (in italics) to illustrate just how far we have come and how far we must go to eliminate this disease.

EPIDEMIOLOGY

The causes of the increasing incidence are necessarily difficult to determine, but many factors have been held responsible by different observers. Influenza, with its effects on bronchial mucosa of atypical regeneration, metaplasia, and cell-nest formation, has been widely suggested as a predisposing cause. On the other hand, Iceland, where carcinoma is, or rather was, unknown, has suffered from severe epidemics of influenza. Other factors such as smoking, exhaust gases from motor vehicles, and tar particles from roads have all been held responsible; but the whole matters is difficult of proof, and it is probable that these are factors which prepare the soil rather than sow the seed.[1]

Incredibly, in 1946 there was little suspicion of the strong association between cigarette smoking and the development of lung cancer. That all changed when the British researchers Doll and Hill provided the landmark article on the risk of lung cancer and cigarette smoking in 1950.[2] This was followed by the US Surgeon General's report in 1964 which strongly recommended that those who smoke should stop and those who hadn't started should not.[3] Since the release of that publication there has been a steady decline in cigarette smoking in developed nations. There has also been a proportional decrease in lung cancer rates which lagged approximately 20 years behind. In 1998 the age adjusted death rate per 100 000 population for men had reached a high of 75.5 in Scotland, which is one of the highest rates in all of the European countries.[4] The lowest rates of lung cancer can be found in South America and Africa.[5–7] For example, in 1994 the rate of lung cancer in Africa was about 5 per 100 000 people. This compares with the rates found in the United States in the 1930s which was before the beginning of the epidemic in lung cancer.

There are several disturbing trends in the epidemiology of lung cancer. Developing nations have begun to increase their smoking rates and consequently the incidence rates of lung cancer have begun to rise. China, for example, reported 800 000 cases of lung cancers in 1998.[8 9] Nearly one third of the world's smokers reside in China. The average number of cigarettes smoked by each adult male in China is 11 per day, which is a rate equivalent to that of the highest rates ever seen in developed nations, which coincidentally were seen at the end of World War II. Another disturbing trend in lung cancer is the increasing incidence of lung cancer among women.[10] More women in developed nations will die of lung cancer than of breast cancer. Because of historical cigarette smoking patterns, the incidence rates of lung cancer in women have yet to decline because smoking rates in this group had peaked later than men.[11] Currently, far more men than women die from this disease, but the gender gap in lung cancer mortality is steadily narrowing and will eventually close.[12] With regard to socioeconomic status, lung cancer is more likely to occur in the poor and less educated—a pattern observed in many countries worldwide.[13] To summarise, the incidence of lung cancer is falling in developed countries, rising in developing countries, declining in men, and levelling off in women. The poor and the minorities remain at risk because smoking rates remain high in these groups. Primary prevention and smoking cessation must be directed at these high risk groups.

SCREENING

Early diagnosis still offers considerable difficulties, not so much once the patient has reached the practitioner but, owing to the fact that many cases of the disease are relatively symptomless, or with so insignificant or unassessable a symptom as lassitude, until late in the

See end of article for authors' affiliations

Correspondence to: Dr G A Silvestri, Division of Pulmonary and Critical Care Medicine, 96 Jonathan Lucas Street, Suite 812, P O Box 250623, Charleston, SC 29425, USA; silvestri@musc.edu

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disease. As we all know, in many cases the secondary deposits give the first symptoms, such as those of cerebral tumour, loss of voice due to recurrent laryngeal palsy, urgent dyspnea due to a large pleural effusion, or even direct extension to the heart, suggesting coronary occlusion. At this stage operative treatment is out of the question and radiotherapy of questionable value.[1]

Even then, Tudor Edwards recognised the vexing dilemma associated with patients who present with lung cancer—that is, that they present late in the course of the disease when surgical resection is usually not possible. Thus, screening for lung cancer has been an attractive concept. In the 1970s and 1980s, screening by chest radiography was studied extensively.[14–16] Unfortunately, the randomised trials using chest radiography failed to show a reduction in lung cancer mortality in the screened group. These studies were highly criticised for being both underpowered and having high contamination rates in the control group. There has recently been a resurgence in interest in screening with low dose computed tomographic (CT) scanning, with several uncontrolled trials using low dose spiral CT.[17–19] These have shown that spiral CT scanning detects more lung cancers than chest radiography, but also has a high prevalence of benign non-calcified pulmonary nodules. The low dose CT trials have shown a stage shift—that is, more cases of early stage disease. One would presume that this would lead to better outcomes with surgical resection. However, from these studies it is impossible to determine whether this is due to bias (lead time, length, or overdiagnosis) or a true reduction in mortality.[14] Randomised controlled trials are currently underway both in the United States and Europe. The National Lung Screening trial in the US has randomised 50 000 high risk participants to either yearly CT scanning or chest radiography. Subjects have been screened for 3 years and are currently being followed up for another 5 years. While there is much excitement about the possibility of detecting lung cancer in its earliest and perhaps most curable stage, currently the evidence does not advocate for screening for lung cancer outside of clinical trials.[14]

STAGING

Imaging

Radiological examination should never be omitted, but it must be recognized that a carcinoma can occur in one of the larger bronchi without any radiological change in the lung, provided there is insufficient obstruction to interfere with the free inflow and outflow of air to and from the lung beyond. In the majority of cases, however, a shadow will be evident on the film… Enlarged glands are almost invariably present, and it is by no means always easy to determine whether the enlargement is due to infection, secondary growth, or a combination of both. When the glands are enlarged by secondary growth, as is sometimes obvious, the ultimate prognosis is adversely affected, even when all visible glands are removed.[1]

Perhaps the most important advances in the evaluation of patients with lung cancer have come from better ability to stage patients accurately. The staging classification is extremely important because the correct stage provides both prognostic information and a framework for treatment. It has never been more important than recently, as each stage of this disease is now treated very differently. For example, stage I non-small cell lung cancer is treated with surgery alone; stage II with surgery followed by adjuvant chemotherapy; stage IIIA lung cancer is usually treated with a combination of chemotherapy and radiation; and metastatic lung cancer is treated with chemotherapy alone or best supportive care. Unfortunately, none of our non-invasive radiological tests or invasive staging examinations is infallible.[20]

The staging of lung cancer should start with a CT scan of the chest down to and including the adrenal glands. The CT scan is important because it gives us information about tumour size (T status), lymph node size and location (N status), and perhaps information regarding metastasis both within and outside the chest. Unfortunately, the test characteristics for CT scans in the mediastinum are wholly inadequate. Nearly 40% of the lymph nodes that are deemed enlarged by chest CT scanning are found not to contain cancer when they are sampled using either mediastinoscopy or at the time of surgery.[21] Thus, further evaluation is almost always necessary. A modality for staging lung cancer which is gaining wider acceptance is the use of positron emission tomography (PET), which is based on the biological activity of neoplastic cells. Lung cancer cells have increased cellular uptake of glucose and a higher rate of glycolysis than normal cells. The radiolabelled glucose analogue to ^{18}F-fluoro-2-deoxy-D-glucose (FDG) accumulates in cells that have high glucose utilisation and can then be identified with a PET camera. The test characteristics for PET are much better than CT scans for the mediastinum. However, a false positive rate of 12–15% can be expected. It is therefore imperative to sample mediastinal lymph nodes to document cancer in association with a positive PET scan before deeming the patient unresectable.[20]

Several trials of PET have shown that futile thoracotomies could be avoided in about 20% of patients previously believed to be resectable.[22 23] New generation integrated PET-CT machines may combine the advantages of both studies and outperform either test alone, but there are as yet few studies addressing the accuracy of this modality.[24]

To summarise, all patients who are well enough to be considered for treatment for lung cancer should undergo a CT

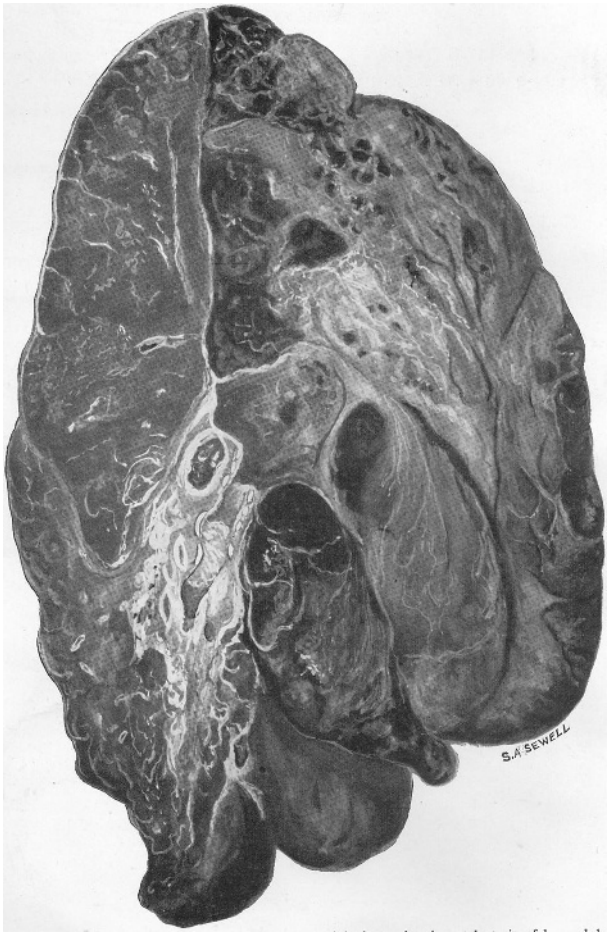

Figure 1 from paper by Edwards, *Thorax* 1946;**1**:1–25. Carcinoma of lower and middle lobes right lung, showing atelectasis of lower lobe and distension due to partial obstruction in middle lobe.

scan of the chest and upper abdomen to help delineate the anatomical location of the primary tumour, the presence of enlarged mediastinal lymph nodes, and metastatic deposits both within and outside the chest. Where available, but particularly in preoperative patients, a PET scan should be performed to assess increased functional activity in the tumour, lymph nodes, or metastatic foci. Abnormal findings on imaging studies should not be accepted without tissue confirmation as false positive findings, if accepted, will misclassify the patient, thus leading to suboptimal care.

Invasive staging

Bronchoscopy should never be omitted. The movements of the vocal cords are visualized, and either a growth projecting into the lumen of the main lobar bronchi or early secondary lobar bronchi may be seen, and a specimen removed for biopsy or submucous infiltration and narrowing of the bronchi observed. Occasionally, a bulging causing deformity without involvement of the bronchial mucosa is the only visible lesion.[1]

Many modalities are available to confirm the diagnosis and stage of lung cancer. Bronchoscopy can both diagnose and stage patients with lung cancer simultaneously. More than 50% of patients with advanced stage lung cancer will have involvement of the central airways in the form of bulky endobronchial disease, endobronchial extension, or extrinsic compression of the airways by the tumour or by lymphadenopathy.[25] In those with endobronchial lesions, the yield with three or more biopsies should approach 100% for centrally located lesions.[26 27] Endobronchial biopsies provide the highest sensitivity (0.74; range 0.48–0.97), followed by brushings (0.59; range 0.23–0.93) and washings (0.48; range 0.29–0.78). Overall, the sensitivity of all bronchoscopic techniques for the diagnosis of centrally located endobronchial lesions is reported as 0.88 (range 0.67–0.97, 30 studies) In the case of lung cancer which presents with submucosal infiltration or extrinsic compression from peribronchial disease, endobronchial forceps biopsy has a lower yield (55%) than transbronchial needle aspiration (71%).

Historically, staging the mediastinum has been performed by mediastinoscopy, anterior mediastinotomy, and ultimately by thoracotomy which remains the ''gold standard''.[28] These techniques may become less commonly employed with the advent of minimally invasive techniques such as transbronchial needle aspiration (TBNA) and endoscopic ultrasound (EUS) which, in the right setting, can approach the diagnostic yield of standard mediatinoscopy or mediastinotomy.[29] The use of TBNA in staging lung cancer has been reported to be moderately sensitive and highly specific in diagnosing the spread of cancer to lymph nodes. In a recently published meta-analysis, the sensitivity of blind TBNA for non-small cell lung cancer was 39–78% but depends greatly on the prevalence of cancer in the lymph nodes and the quality of the study reporting the data. The specificity is reported at 99%.[30] Several studies over the past few years have reported exciting findings with the use of endobronchial ultrasound (EBUS) with fine needle aspiration to stage lung cancer.[31 32] The largest study of EBUS included more than 500 patients at multiple sites and the accuracy rivalled mediastinoscopy with a sensitivity of 94% and a specificity of 100%.[31 32] The most important caveat of invasive staging is the absolute requirement that tissue should be obtained by whatever means available to confirm the findings discovered on non-invasive imaging.

TREATMENT

Surgery

Preoperative evaluation

The proportion of cases operated upon to those in whom the lobe or lung can be removed must necessarily be high. Two factors must essentially be taken into account when the question arises—the general condition of the patient and the local condition. The general condition will depend upon such factors as age, condition of cardiovascular and respiratory systems, associated conditions, such as diabetes, etc. Age is dependent upon so many variables that of itself it is not of supreme importance.[1]

Surgery is the best option for lung cancer cure. Unfortunately, the predisposing condition which causes most lung cancers (smoking) is a major risk factor for additional cardiopulmonary diseases (COPD, coronary and vascular disease) that place patients at high risk for a poor outcome. The difficulty for the clinician is weighing the risks of perioperative death and long term disability against the reward of the long term survival that surgical resection can provide.[33 34]

There are several guidelines available to assist the clinicians in this evaluation. In general, following the guidelines will help assess the risk. However, they do not replace individual clinical judgement and patient preference. There are several important caveats to the guidelines. Firstly, this evaluation is best done with the respiratory physician in conjunction with a thoracic surgeon. This will provide the best assessment of risk as well as lung sparing surgical options—for example, sleeve lobectomy or wedge resection—in those who are candidates. Secondly, as Tudor Edwards pointed out 60 years ago, age alone is not a contraindication to surgery. It is estimated that, in 2005, 40% of those diagnosed with lung cancer will be more than 75 years old.[35] The mortality from lobectomy and pneumonectomy in those aged over 70 years is 4–7% and 14%, respectively.[34 36] In one study of 68 patients aged over 80, the mortality was an acceptable 8.8%.[37] Finally, patient preference needs to be incorporated into decision making. Some patients may be risk adverse and accept lesser opportunities for cure, while others may accept higher perioperative mortality for a better long term survival.

Lobectomy and pneumonectomy—In my opinion pneumonectomy should be carried out in every case where conditions permit. In no case of mine in which lobectomy has been performed for carcinoma has a patient survived over three years.[1]

This above recommendation has undergone the most revision in the past 60 years. It is likely that Tudor Edwards faced more cases of advanced disease which required pneumonectomy to obtain tumour free surgical margins. Surgery is the treatment modality of choice for stage 1 and 2 lung cancer.[38 39] However, with better staging and operative technique, lobectomy with lymph node dissection is the surgery of choice when possible. The perioperative mortality is less than 5% for lobectomy as opposed to around 10% for pneumonectomy. A full anatomical resection is better than a ''wedge'' resection as the local recurrence rate is higher for those who undergo a wedge resection.[40]

Radiotherapy

X-ray therapy some years ago produced such general reactions as not to warrant submitting patients to the treatment, as so many were made more miserable than if left alone. In the last six years sufficient improvement has resulted to warrant the subjection of inoperable cases to this treatment with distinct hopes of amelioration of symptoms, disappearance of the radiological shadows in some cases, and prolongation of useful life. Nevertheless, I have yet to see a proven case of carcinoma of the bronchus cured by this measure.[1]

Radiotherapy remains a predominantly palliative treatment and a very effective one for bone pain, haemoptysis, dyspnoea, and skin nodules and shrinkage of palpable nodes. Its ability to cure remains disappointing. Despite advances in dose application with improved collimation, patient immobilisation and portal imaging allowing the radical dose to increase towards 100 Gy, the 5 year survival rates remain less than 10%. The biggest improvement in radiation treatment

was the development of continuous hyperfractionated accelerated radiotherapy (CHART) which improved the overall 5 year survival from 7% to 12%, with a bigger advantage for patients with squamous cell cancers.[41] However, this technology has not been accepted as manageable in the general practice of busy radiotherapy departments in most countries.

The potential of adding chemotherapy to radical radiotherapy in locally advanced disease has been assessed as a neoadjuvant and as a concurrent treatment, with a small improvement in median survival and a suggestion that concurrent chemo-irradiation is better than sequential approaches.[42]

Giving radiotherapy postoperatively has been shown to be deleterious to survival. A meta-analysis of more than 2000 patients in nine randomised trials of postoperative radiotherapy showed a decrease in survival of 7% at 2 years, especially in those with earlier stage disease.[43] It has to be hoped that this potentially effective treatment will become more useful as the technology around its application continues to improve. However, a recent assessment of more than 7000 patients given postoperative radiotherapy or just observation, but not in randomised trials, showed no clear advantage for the addition of radiotherapy. In a subgroup analysis there was a small significant advantage for those with N2 disease.[44]

Chemotherapy in non-small cell lung cancer (NSCLC)

After the early encouraging improvement in the median survival in small cell lung cancer (SCLC), attention turned to NSCLC in the middle 1980s. Since then some progress has been made in terms of longer survival, and some important questions are being addressed. In general, the response rate to chemotherapy is much lower than in SCLC, probably as the cell type is much less aggressive, with fewer cells in the vulnerable part of their cell cycle. A complete response is rarely seen and only up to 40% of subjects gain a partial response with modern day chemotherapy.

Chemotherapy has been extensively studied in advanced NSCLC. Initially, responses to chemotherapy occurred in 10–15% of cases with only a 6 week extension to median survival.[45] These results were from older cisplatin containing regimens. Newer agents such as gemcitibine, taxols, and vinorelbine have extended the survival advantage to 3–4 months compared with best supportive care alone. While no particular combination stands out, results for treatment with at least four courses of chemotherapy will provide a median survival of 8–10 months compared with 4–5 months without chemotherapy, and a 1 year survival of 40% compared with 18%.[46] The main advantage of modern chemotherapy is its better toxicity profile with less nausea, vomiting, hair loss, and neutropenic sepsis. Also, for the responding population, there is an improvement in quality of life.[47 48] Despite these apparent advantages for giving chemotherapy to patients presenting with advanced disease, there is still a substantial refusal rate and concern among patients.[49] It is only really suitable for subjects with good performance status (ECOG 0–1) as the responses and progression-free interval are less in patients with a performance status of ECOG 2 and toxicity greater. Despite the increasing age at presentation of lung cancer patients, with more than 40% being over 70 years of age, there are still few studies focusing on the elderly and their responses to chemotherapy.[50] Furthermore, as with many common diseases, much of the available data come from trials in which less than 10% of the study population are elderly.

The potential for chemotherapy to improve survival around surgery has become clearer. The NSCLC Collarborative Group meta-analysis in 1995 suggested a 5% advantage for chemotherapy around surgery. Most of the randomised studies included were of adjuvant chemotherapy and with platin containing regimens.[45] However, the differences were not significant and several studies have re-addressed this question. Studies assessing adjuvant chemotherapy have included large numbers of patients[51 52] and others fewer.[53 54] All but two were positive in favour of adjuvant chemotherapy and a meta-analysis of the five largest trials entering more than 300 patients (total of 4584 patients) has shown a significant 5.3% advantage in median survival for chemotherapy.[55] It is likely that adjuvant chemotherapy will become a standard choice for patients following a curative resection and should be routinely offered to those who have had a curative resection. There is still some debate as to the utility of adjuvant therapy for the earliest stage disease (stage 1A and B). However, there is clear evidence in favour of its use in those with resected stage 2 and 3A disease.

There is no such clarity for the value of neoadjuvant chemotherapy. Two small studies found strikingly in favour of neoadjuvant therapy,[56 57] but a much larger study[58] found no advantage. Other studies are due to complete soon and a clearer message may emerge as to whether neoadjuvant chemotherapy has value.

Treatment of small cell lung cancer

This cell type remains a deadly and frustrating disease which, in the mid 1970s, began to appear treatable and even curable by chemotherapy. Small cell lung cancers comprise 20–25% of lung cancers,[59] are almost entirely smoking related, aggressive, with an extensive list of presenting symptoms and paramalignant syndromes. Like most lung cancers, it was first considered to be a surgical option, but the earliest studies of surgery were disappointing,[60 61] and then it fared badly in comparison with radical radiotherapy.[62] Once tumour staging became more accurate with the development of CT scanning, it became clear that 60% of cases presented with extensive disease and even those with limited disease had involvement of the mediastinal structures, effusions, and often involved the whole lung, making surgery impossible.

Initial studies in the 1970s with one and then two or three cytotoxic agents in combination showed surprisingly high response rates to chemotherapy with acceptable toxicity.[63 64] The median survival rose from 2–3 months untreated for extensive disease and 4–6 months for limited disease, to 6 and 9–12 months, respectively. Subjects were initially treated until a complete response was obtained and then for a further year, while those achieving only a partial response continued chemotherapy until relapse. This was hard for patients to tolerate and studies then addressed the optimal duration for chemotherapy and found that six courses of combination chemotherapy was adequate, with median survival reaching 18 months and 9 months for limited disease and extensive disease, respectively.[65 66]

Unfortunately, the next 20 years have added little to the outcomes for this cell type, and it has faded from the front line of research. However, refinements of treatment have occurred. After several trials assessing the value of adding radiotherapy to the primary site and the mediastinum following chemotherapy produced mixed results, a meta-analysis showed a significant (4%) survival advantage at 2 years for the addition of radiotherapy in patients with limited disease.[67 68] Subsequent trials to ascertain whether the radiotherapy should be given early during chemotherapy or late (towards the end of chemotherapy) failed to provide a clear answer. It now seems most important to ensure that chemotherapy is delivered as intended, and the timing of radiotherapy is less important.[69] Similarly, the total dose of radiotherapy and its intensisty (daily or twice daily fractions) may be of secondary importance.

Many trials attempted to improve survival for patients with limited disease, in particular by dose intensification. These included very high dose chemotherapy with prior bone marrow harvest and re-infusion after chemotherapy,[70] weekly versus conventional 3 weekly schedules,[71] early and late dose intensification of chemotherapy,[72] and bone marrow stimulation with colony growth stimulating factors.[73] However, there was no worthwhile improvement compared with conventional regimens in similar patient groups.

Other refinements have included the recognition of the dangers of chemotherapy induced sepsis and death in patients presenting with widespread disease,[74] and that broad spectrum antibiotics prevent these unnecessary deaths. Also, the early identification of those likely to respond well and become long term survivors using simple parameters including performance status and routine biochemistry has provided prognostic factors to identify those who will benefit most from chemotherapy,[75] Prophylactic cranial irradiation will reduce the incidence of relapse in the brain and prolong a better quality of life,[76] especially in patients who achieve a complete response following chemotherapy.

Second line chemotherapy has been explored with disappointing results, with most tumours resistant to further schedules or, at best, achieving a low incidence of partial response. Topotecan has recently been reported with some promise.[77] It is almost tragic that, in a tumour type that responds so massively to first line chemotherapy with 85% of patients experiencing a partial or complete response, so little has been achieved.

Growth modifying agents

With chemotherapy reaching a plateau for NSCLC, new data has emerged on so-called 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 a target for new therapies. Two oral inhibitors of EGFR (gefitinib and erlotinib) have been studied in detail, mainly in advanced NSCLC. Two randomised studies of gefitinib in different doses have been reported in patients who had relapsed after 1–4 chemotherapy regimens.[78 79] Although not placebo controlled, both trials showed tumour activity, responses, and improvements in quality of life. A further trial in relapsed advanced disease of gefitinib versus placebo showed trends to better survival, but this was not significant.[80] Erlotinib has also been studied in patients with advanced disease who had relapsed after one or two regimes of chemotherapy and were then randomised to receive placebo or erlotinib. There was a significant survival advantage over placebo for erlotinib with a 4 month prolongation of disease control despite only 8.9% of the treated population showing a response to erlotinib. Overall survival was extended by 2 months for the erlotinib group (6.7 *v* 4.7 months).[81] This agent has become the recommended second line treatment in some countries and awaits review in the UK. It appeared especially effective after subgroup analyses in Asian women with adenocarcinoma who had never smoked. Other targeted treatments are in preparation, and growth modification after initial chemotherapy may offer new treatment possibilities.

CONCLUSIONS

So, 60 years after Tudor Edwards' first paper in appeared in *Thorax*, how far have we travelled? Screening for lung cancer is undergoing intense study but the answer as to whether it can reduce mortality is not yet known and won't be for another 5 years or so. Staging has advanced greatly and is paramount in case selection for treatment. We know that surgery remains the best chance for cure, but lobectomy or more refined lung conserving resections are preferred as so many sufferers also have COPD. Chemotherapy for small cell lung caner, exciting in the 1970s and 1980s, has ground to a halt and much effort is required to stimulate research into this cell type which represents 20% of lung cancers, as it appeared potentially curable. The less responsive NSCLC has seen that advances in treatment and adjuvant chemotherapy are likely to be a choice for stage II and IIIA patients after resection. For advanced disease, chemotherapy is a palliative tool with a modest effect in extending survival. The potential of EGFR antagonists and other ''targeted agents'' may have great potential but are yet to be fully explored. More importantly, they signal a shift in how lung cancer treatment is likely to be attacked from the therapeutic side in years to come. Finally, what Tudor Edwards was not so certain about in 1946 has become only too clear over the last half century. The impact of tobacco, although curbed in some countries, is surely going to fan the flames for decades to come.

Authors' affiliations

G A Silvestri, Medical University of South Carolina, Charleston, SC, USA
S G Spiro, Department of Thoracic Medicine, Middlesex Hospital, London, UK

REFERENCES

1 **Edwards AT**. Carcinoma of the bronchus. *Thorax* 1946;**1**:1–25.
2 **Doll R**, Hill A. Smoking and carcinoma of the lung. *BMJ* 1950;**2**:739–48.
3 **US Department of Health Education and Welfare**. *Smoking and health: report of the advisory committee to the Surgeon General of the Public Health Service*. Washington, DC: US Government Printing Office, 1964.
4 **National Cancer Institute**. Cancer rates and risks: Cancer Statistics Branch Division of Cancer Prevention and Control. Bethesda, MD: National Institutes of Health, 1996.
5 **Gordon T**, Crittenden M, Haenszel W. Cancer mortality trends in the United States, 1930–1955. *Natl Cancer Inst Monogr* 1961;**6**:131–350.
6 **Parkin DM**, Muir CS, Whelin SL, *et al*. *Cancer incidence in five continents*. Lyon, France: International Agency for Research on Cancer, 1992.
7 **Parkin DM**, Pisani P, Lopez AD, *et al*. At least one in seven cases of cancer is caused by smoking. Global estimates for 1995. *Int J Cancer* 1994;**59**:494–504.
8 **Liu BQ**, Peto R, Chen ZM, *et al*. Retrospective proportional mortality study of one million deaths. *BMJ* 1998;**317**:1411–22.
9 **Pandey M**, Mathew A, Nair MK. Global perspective of tobacco habits and lung cancer: a lesson for third world countries. *Eur J Cancer Prev* 1999;**8**:271–9.
10 **American Cancer Society**. *Cancer facts and figures*. Atlanta, GA: American Cancer Society, 2006.
11 **Ries LAG**, Miller BA, Hankey BF, *et al*. Cancer statistics review: 1973–1993. Bethesda, MD: US Government Printing Office, 1995.
12 **Jemal A**, Travis WD, Tarone RE, *et al*. Lung cancer rates convergence in young men and women in the United States: analysis by birth cohort and histologic type. *Int J Cancer* 2003;**105**:101–7.
13 **Schwartz KL**, Crossley-May H, Vigneau FD, *et al*. Socioeconomic status and stage at diagnosis for five common malignancies. *Cancer Causes Control* 2003;**14**:761–6.
14 **Bach P**, Niewwoehner D, Black W. Screening for lung cancer: the guidelines. *Chest* 2003;**123**:83–8S.
15 **Fontana RS**, Sanderson DR, Woolner LB, *et al*. Lung cancer screening. The Mayo Program. *J Occup Med* 1986;**28**:746–50.
16 **Marcus P**, Bergstralh E, Fagerstrom R, *et al*. Lung cancer mortality in Mayo Lung Project: impact of extended follow up. *J Natl Cancer Inst* 2000;**92**:1308–16.
17 **Henschke C**, McCauley D, Yankelevitz D, *et al*. Early lung cancer detection project: overall design and findings from baseline screening. *Lancet* 1999;**354**:99–105.
18 **MacRedmond R**, Logan PM, Lee M, *et al*. Screening for lung cancer using low dose CT scanning. *Thorax* 2004;**59**:237–41.
19 **Swensen S**, Jett J, Hartman T, *et al*. Lung cancer screening with CT: Mayo Clinic experience. *Radiology* 2003;**226**:756–61.
20 **Silvestri GA**, Tanoue LT, Margolis ML, *et al*. The noninvasive staging of non-small cell lung cancer: the guidelines. *Chest* 2003;**123**:147–56s.
21 **McLoud T**, Bourgouin P, Greenberg R, *et al*. Bronchogenic carcinoma: analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. *Radiology* 1992;**182**:319–23.
22 **Pieterman RM**, van Putten JWG, Meuzelaar JJ, *et al*. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *N Engl J Med* 2000;**343**:254–61.
23 **Reed CE**, Harpole DH, Posther KE, *et al*. Results of the American College of Surgeons Oncology Group Z0050 trial: the utility of positron emission tomography in staging potentially operable non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2003;**126**:1943–51.

24 **Lardinois D**, Weder W, Hany TF, *et al*. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *N Engl J Med* 2003;**348**:2500–7.
25 **Simoff MJ**. Endobronchial management of advanced lung cancer. *Cancer Control* 2001;**8**:337.
26 **Popovich J**, Kvale PA, Eichenhorn MS, *et al*. Diagnostic accuracy of multiple biopsies from flexible bronchoscopy. *Am Rev Respir Dis* 1982;**125**:521.
27 **Shure D**, Astarita R. Bronchogenic carcinoma presenting as an endobronchial mass. *Chest* 1983;**83**:865–7.
28 **Detterbeck FC**, DeCamp MM, Kohman L, *et al*. Invasive staging: the guidelines. *Chest* 2003;**123**:167–75s.
29 **Wallace MB**, Silvestri GA, Sahai AV, *et al*. Endoscopic ultrasound-guided fine needle aspiration for staging patients with carcinoma of the lung. *Ann Thorac Surg* 2001;**72**:1861–7.
30 **Holty JE**, Kuschner WG, Gould MK. Accuracy of transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: a meta-analysis. *Thorax* 2005;**60**:949–55.
31 **Herth FJ**, Lunn W, Eberhardt R, *et al*. Transbronchial versus transesophageal ultrasound-guided aspiration of enlarged mediastinal lymph nodes. *Am J Respir Crit Care Med* 2005;**171**:1164–7.
32 **Herth FJ**, Eberhardt R, Vilmann P, *et al*. Real-time endobronchial ultrasound-guided transbronchial needle aspiration: a new method for sampling mediastinal lymph nodes. *Thorax* 2006;**61**:795–8.
33 **Beckles MA**, Spiro SG, Colice GL, *et al*. The physiologic evaluation of patients with lung cancer being considered for surgery. *Chest* 2003;**123**:105–14S.
34 **British Thoracic Society, Society of Cardiothoracic Surgeons of GB & Ireland Working Party**. Guidelines on the selection of patients with lung cancer for surgery. *Thorax* 2001;**56**:89–106.
35 **Brown JS**, Eraut D, Trask C, *et al*. Age and the treatment of lung cancer. *Thorax* 1996;**51**:564–8.
36 **Damhuis RA**, Schutte PR. Resection rates and postoperative mortality in 7,899 patients with lung cancer. *Eur Respir J* 1996;**9**:7–10.
37 **Brock MV**, Kim MP, Hooker CM. Pulmonary resection in octogenarians with stage I nonsmall cell lung cancer. *Ann Thorac Surg* 2004;**77**:271–7.
38 **Scott WJ**, Howington J, Movsas B. Treatment of stage II non-small cell lung cancer. *Chest* 2003;**123**:188–201S.
39 **Smythe WR**. Treatment of stage I non-small cell lung carcinoma. *Chest* 2003;**123**:181–7S.
40 **Ginsburg R**, Rubinstein L. A randomized comparative trial of lobectomy vs limited resection for patients T1N0 non-small cell lung cancer. *Lung Cancer* 1995;**7**:83–8.
41 **Saunders M**, Dische S, Barrett A, *et al*. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: a randomized multicentre trial. *Lancet* 1997;**350**:161–5.
42 **Price A**. Lung cancer – 5: State of the art radiotherapy for lung cancer. *Thorax* 2003;**58**:447–52.
43 **PORT Meta-Analysis Trialists Group**. Post operative radiotherapy in non-small cell cell lung cancer: systemic review and meta-analysis of individual patient data from nine radomized controlled trials. *Lancet* 1998;**352**:257–63.
44 **Lally BE**, Zelterman D, Colasanto JM, *et al*. Impact of post operative radiotherapy for patients with stage II–III non-small-cell lung cancer using the Surveillance, Epidemiology, and End Results Database. *J Clin Oncol* 2006;**24**:2998–3006.
45 **Non-Small Cell Lung Cancer Collaborative Group**. Chemotherapy in non-small cell lung cancer:a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995;**311**:899–909.
46 **Schiller J**, Harrington D, Belani C, *et al*. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. *N Engl J Med* 2002;**346**:92–8.
47 **Thongprasert S**, Sanguanmitra P, Juthapan W, *et al*. Relationship between quality of life and clinical outcomes in advanced non-small cell lung cancer: best supportive care (BSC) versus BSC plus chemotherapy. *Lung Cancer* 1999;**24**:17–24.
48 **Spiro SG**, Rudd RM, Souhami RL, *et al*. Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life. *Thorax* 2004;**59**:828–36.
49 **Spiro S**, Gower N, Evans M, *et al*. Recruitment of patients with lung cancer into a randomised clinical trial: experience at two centres. On behalf of the Big Lung Trial Steering Committee. *Thorax* 2000;**55**:463–5.
50 **Booton R**, Jones M, Thatcher N. Lung cancer – 7: Management of lung cancer in elderly patients. *Thorax* 2003;**58**:711–20.
51 **Arriagada R**, Bergman B, Dunant A, *et al*. International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;**350**:351–60.
52 **Scagliotti GV**, Fossati R, Torri V, *et al*. Randomised study of adjuvant chemotherapy for completely resected stage I, II, IIIA non-small cell lung cancer. *J Natl Cancer Inst* 2003;**95**:1453–61.
53 **Winton T**, Livingston R, Johnson D, *et al*. National Cancer Institute of Canada Clinical Trials Group. National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005;**352**:2589–97.
54 **Waller D**, Peake MD, Stephens RJ, *et al*. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. *Eur J Cardiothorac Surg* 2004;**26**:173–82.
55 **Pignon JP**, Tribodet H, Scagliotti GV, *et al*. Lung Adjuvant Cisplatin Evaluation : a pooled analysis of five randomized clinical trials including 4,584 patients. *ASCO*, 2006; abstract, 7008;(LACE).
56 **Rosell R**, Gomez-Codina J, Camps C, *et al*. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small cell lung cancer. *N Engl J Med* 1994;**330**:153–8.
57 **Roth J**, Fossella F, Komaki R, *et al*. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small cell cell lung cancer. *J Natl Cancer Inst* 1994;**86**:673–80.
58 **Depierre A**, Milleron B, Moro-Sibilot D, *et al*. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small cell lung cancer. *J Clin Oncol* 2002;**20**:247–53.
59 **Simon GR**, Wagner H. Small cell lung cancer. *Chest* 2003;**123**:259–71S.
60 **Lennox SC**, Flavell G, Pollock DJ, *et al*. Results of resection for oat-cell carcinoma of the lung. *Lancet* 1968:925–7.
61 **Shields TW**, Higgins GA, Matthews MJ, *et al*. Surgical resection in the management of small cell lung cancer *J Thorac Cardiovasc Surg* 1982;**84**:481–8.
62 **Working Party on the Evaluation of Different Methods of Therapy in Carcinoma of the Bronchus**. Comparative trial of surgery and radiotherapy for the primary treatment of small-celled, or oat celled carcinoma of the bronchus. *Lancet* 1966;**2**:979–86.
63 **Lowenbraun S**, Bartolucci A, Smalley RV, *et al*. The superiority of combination chemotherapy over single agent chemotherapy in small cell lung carcinoma *Cancer* 1979;**44**:406–13.
64 **Cohen M**, Creaven P, Fossieck B Jr, *et al*. Intensive chemotherapy of small cell bronchogenic carcinoma. *Cancer Treat Rep* 1977;**61**:349–54.
65 **MRC Lung Cancer Working Party**. Controlled trial of twelve versus six courses of chemotherapy in the treatment of small cell lung cancer: report to the Medical Research Council by its Lung Cancer Working Party. *Br J Cancer* 1989;**59**:584–90.
66 **Spiro SG**, Souhami RL, Geddes DM, *et al*. Duration of chemotherapy in small cell lung cancer: a Cancer Research Campaign trial. *Br J Cancer* 1989;**59**:578–83.
67 **Pignon JP**, Arriagada R, Ihde DC, *et al*. A meta-analysis of thoracic radiotherapy in small cell lung cancer. *N Engl J Med* 1992;**327**:1618–24.
68 **Warde P**, Payne D. Does thoracic irradiation improve survival and local control in limited stage small cell carcinoma of the lung? *J Clin Oncol* 1992;**10**:890–5.
69 **Spiro SG**, James LE, Rudd RM, *et al*. Early compared with late radiotherapy in combined modality treatment for limited disease small cell lung cancer: a London Lung Cancer Group multicenter randomized clinical trial and meta-analysis. *J Clin Oncol* 2006;**24**:3823–30.
70 **Souhami R**, Hajichristou H, Miles D, *et al*. Intensive chemotherapy with autologous bone marrow transplantation for small cell lung cancer. *Cancer Chemother Pharmacol* 1989;**24**:321–5.
71 **Souhami R**, Rudd R, Trask C, *et al*. Randomised trial comparing weekly with three weekly chemotherapy in small cell lung cancer: a Cancer Research Campaign trial. *Br J Cancer* 1998;**86**:1157–66.
72 **Ihde D**, Mulshine J, Kramer B, *et al*. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small cell lung cancer. *J Clin Oncol* 1994;**12**:2022–34.
73 **Thatcher N**, Girling D, Hopwood P, *et al*. Improving survival without reducing quality of life in small cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: results of a British Medical Research Council multicenter randomized trial. Medical Research Council Lung Cancer Working Party. *J Clin Oncol* 2000;**18**:395–404.
74 **Morittu L**, Earl H, Souhami R, *et al*. Patients at risk of chemotherapy-associated toxicity in small cell lung cancer. *Br J Cancer* 1989;**59**:801–4.
75 **Souhami R**, Bradbury I, Geddes D, *et al*. Prognostic significance of laboratory parameters measured at diagnosis in small cell carcinoma of the lung. *Cancer Res* 1985;**45**:2878–82.
76 **Auperin A**, Arriagada R, Pignon J, *et al*. Prophylactic cranial irradiation for patients with small cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999;**341**:476–84.
77 **Huber RM**, Reck M, Gosse H, *et al*. Efficiacy of a toxicity-adjusted topotecan therapy in recurrent small cell lung cancer. *Eur Respir J* 2006;**27**:1183–9.
78 **Fukuoka M**, Yano S, Giaccone G, *et al*. Multi-institutional randomized phase II trial of geftinib for previously treated patients with advanced non-small cell lung cancer. *J Clin Oncol* 2003;**21**:2237–46.
79 **Kris MG**, Natale RB, Herbst RS, *et al*. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* 2003;**290**:2149–58.
80 **Thatcher N**, Chang A, Parikh P, *et al*. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005;**366**:1527–37.
81 **Shepherd FA**, Rodrigues Pereira J, Ciuleanu T, *et al*. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;**353**:123–32.