State of the Art

Lung Cancer—Where Are We Today?
Current Advances in Staging and Nonsurgical Treatment

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Lung cancer remains the commonest cause of cancer death in both men and women in the developed world, although mortality rates for men are dropping. Spiral computed tomography (CT) of the chest in middle-aged, smoking subjects may identify two to four times more lung cancers than a chest X-ray, with more than 70% of tumors being Stage I. The incidence of benign nodules is high, making interpretation difficult. Randomized controlled trials are required to determine whether spiral CT detects lung cancer early enough to improve mortality. Preoperative staging has relied on CT scans, but positron emission tomography scanning has greater sensitivity, specificity, and accuracy than CT and is recommended as the final confirmatory investigation when the CT shows resectable disease. In locally advanced non–small cell lung cancer, there is a small advantage for the addition of chemotherapy to radiotherapy, but no advantage for postoperative radiotherapy. Chemotherapy gives no benefit when given as neoadjuvant or adjuvant treatment around surgery. In advanced disease, newer cytotoxic agents confer a small survival advantage over older combinations, but the advantage in median survival over best supportive care remains a few months with modest improvements in quality of life. Survival with small cell lung cancer has shown little increase over the last 15 years despite multiple attempts to manipulate the timing, dose intensity of chemotherapy, and the potential of radiotherapy. Novel therapies are urgently needed for all cell types of lung cancer.

Keywords: chemotherapy; lung cancer; radiotherapy; screening; staging

Lung cancer is one of the most important diseases in respiratory medicine. Worldwide, it is the commonest cancer in men, virtually the commonest in women, and has a greater total incidence than that of colorectal, cervical, and breast cancer combined. In 2001, lung cancer will have caused more than 1 million deaths worldwide and this global incidence is rising at 0.5% per annum. The etiology of the great majority of lung cancers has been known for nearly 50 years (1), but we have failed to make serious inroads into the powerbase of the tobacco industry. In the Western world, although the incidence of lung cancer in men has fallen over the last 20 years, a similar decline among female smokers is not yet evident, and adolescents are smoking in increasing numbers. Global cigarette sales are rising steadily with the ruthless pursuit of new conquests by the tobacco industry in Asia, China, and South America, some of the poorest countries in the world that cannot afford the cost of tobacco-related diseases. In China in 1998, one in four smokers died from tobacco-related causes, and 0.6 million deaths in 1990 were tobacco related, a figure that rose to 0.8 million in 2000 (2).

Lung cancer is a disease for which there is no established screening, which presents late in its course, and has a median survival of 6–12 months from the time of diagnosis with an overall 5-year survival of 5–10%; and yet the major cause of this disease is clearly understood. Communities and countries addressing a smoking ban would probably achieve far more in the long term than we currently are with all our available treatments.

Although surgery offers the best chance of cure in lung cancer, particularly in the case of non–small cell lung cancer, only a small

TABLE 1. AGE-ADJUSTED LUNG CANCER MORTALITY RATES PER 100,000 POPULATION FOR SELECTED COUNTRIES, IN MALES AND FEMALES, 1992–1995

Males		Females	
Country	Lung Cancer Mortality Rate	Country	Lung Cancer Mortality Rate
Hungary	84.0	United States	26.3
Poland	71.4	Denmark	24.9
The Netherlands	64.8	United Kingdom	20.9
Italy	56.2	Hungary	17.9
United States	55.3	China	15.8
United Kingdom	51.8	The Netherlands	12.6
Greece	49.8	Japan	8.3
Germany	47.3	Italy	7.9
France	47.0	Greece	6.9
China	37.3	Mexico	5.8
Japan	31.0		
Mexico	16.1		

Adapted from Schottenfeld D. Etiology and epidemiology of lung cancer. In: Pass HI, Mitchell JB, Johnson DH, Turrisi AT, and Minna JD, editors. Lung cancer. Baltimore, MD: Lippincott-Williams & Wilkins; 2000, p. 369.

proportion of patients are ever suitable for curative resection and the majority must rely on nonsurgical and adjuvant therapies. This review focuses on the role of chemotherapy and radiotherapy in both small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC). In addition, the potential role of screening for lung cancer and advances in staging tests are discussed.

EPIDEMIOLOGY

At the end of the twentieth century, lung cancer had become one of the world's leading causes of preventable deaths. By 1950, case-control epidemiologic studies showed that cigarettes were strongly associated with the risk of lung cancer (3, 4). In 1962, the Royal College of Physicians in London intervened in a public health matter for the first time since 1725 and published a compelling document supporting the evidence that smoking caused lung cancer (5).

Worldwide it is estimated that 47–52% of men and 10–12% of women smoke. Compared with women, men started smoking younger, smoked more and for a longer duration, inhaled more deeply, and bought cigarettes with a higher tar content (6, 7). Women took up smoking in the United States and Western Europe during the second World War. Recent case-control studies have shown female smokers to have a higher relative risk of lung cancer than males, after adjusting for age and average daily consumption.

The incidence of lung cancer shows marked geographical variation, and is most common in developed countries and less so in developing countries, for example, those of Africa and South America (8). The low rates in these countries will inevitably rise to match those of the developed world. Within countries, lung cancer incidence among men considerably exceeds that of women, but the highest rates occur in the same regions for both sexes (Table 1). Only 5–10% of all lung cancers are diagnosed in patients under the age of 50 years, with adenocarcinoma and a positive family history being common in these cases.

The mortality rates for lung cancer closely parallel the incidence rates because of poor survival. Age-adjusted mortality rates increase exponentially until the age of 80 years in men and 70 years in women and then decline. In the United States, lung cancer accounts for 28% of all cancer deaths each year. Whereas it was responsible for 3% of all female cancer deaths in 1950, it accounted for 24% in 1995. The age-adjusted lung cancer death rate passed that of breast cancer among white women in the United States in 1986, and among black women in 1990

(9). However, there is mounting evidence that at least in the developed world death rates from lung cancer may have peaked. Between 1973 and 1994, the incidence of lung cancer in the United States for those over 65 years of age increased by 220% in women, but fell by 18% in men (10). For those under 65 years of age, the incidence of lung cancer increased by 58% in women and fell by 16% in men over the same period (10), and for those younger than 45 years old, age-adjusted incidence and mortality rates from lung cancer fell in both sexes (more so for men) with a projection that, in the United States, overall incidence of and mortality from the disease may begin a decline for both sexes at the beginning of the new millennium (11).

Although lung cancer incidence has fallen in the United States, it remains the leading cause of cancer deaths worldwide, with a global incidence that continues to rise. There is also concern in the United States that the incidence of the disease may start to increase again as a result of increasing tobacco consumption (12). In addition, shifts have occurred in the incidence rates of the different histologic subtypes of lung cancer, with adenocarcinoma surpassing squamous cell tumors as the most frequent type in both white and black Americans.

SCREENING

Chest X-Ray and Sputum Cytology

There has been much interest in the idea of screening to detect presymptomatic lung cancers, when presumably they would be at an earlier and more curable stage of their growth. In the 1970s there was a major effort, using chest X-ray and sputum cytology, to assess the prevalence of tumors and demonstrate that early detection would enhance survival and ultimately decrease mortality. The Mayo Lung Project (13), the Czechoslovakian Screening Study (14), and similar trials at Johns Hopkins Hospital (15) and Memorial Sloan-Kettering Hospital (16) all enrolled male smokers and variously compared annual or more frequent chest X-rays with or without additional sputum cytologic evaluation against a control group who had an initial or annual chest X-ray only. All these studies identified more tumors in the screened than control groups. The tumors were smaller, of a lower (more favorable) stage, and the resection rate and 5-year survival rates were better. However, overall mortality was not improved. Although all these were randomized controlled trials, only the Mayo Lung Project had a true control group that was unscreened. However, this study lacked power from the outset, with less than 20% power to detect a 10% benefit in lung cancer mortality and

a 55% power to detect a 20% benefit. Moreover, there was further contamination as 55% of the control group had a chest X-ray in the previous year and 73% had a chest X-ray during the last 2 years. Compliance was also a significant problem. Interestingly, the screening seemed rather ineffectual, as the incidence of new tumors provided 206 new cancers, of which only 45 (22%) were resectable, compared with 60% of the prevalence tumors at baseline. One of the problems with these studies may have been the choice of mortality from lung cancer as the end point. It has been argued that all-cause mortality (17) or survival from lung cancer may be less biased end points (18). Indeed, Strauss has performed an important and impressive reanalysis of the Mayo Lung Cohort data. This analysis has shown that although the incidence of lung cancer was higher in the screened group, the survival of patients with lung cancer was also much higher in this group when compared with the control group; and this increased survival was directly related to tumor resection and therefore not due to overdiagnosis of "pseudo-disease" (18). Strauss argues that the randomization procedure for the Mayo Lung Project was suboptimal, because of unidentified confounding variables (18). So that although we understand a certain amount about the etiology of lung cancer, we still cannot accurately distinguish those 16% of male and 9% of female life-long smokers who will develop the disease from their fellow smokers who will not. Strauss finally lays to rest the years of debate around the Mayo Lung Project and explains the findings without having to resort to the counterintuitive concept of overdiagnosis; screening is worth doing because more resectable cases are picked up and more patients are cured (18). Another problem highlighted from the Mayo study is that of identifying early tumors on the chest X-ray, as 90% of peripheral and 75% of perihilar tumors were visible in retrospect on previous films (19). Quekel and coworkers more recently also reported a 19% miss rate of peripheral tumors, with an average size of 16 mm (20).

Spiral Computed Tomography

The current interest in screening is due to the advent of low-dose spiral computed tomography (CT), using short scanning times of 12 to 15 seconds, with the potential for mass application. To date, several prevalence studies have reported their early findings. They have, however, all examined different numbers of volunteers of different ages, both sexes, mostly smokers, but with a wide range of smoking histories.

1. Kaneko and coworkers (21) studied 1,369 participants, over 50 years of age and with a smoking history of more than 20 pack-years. Eighty-two percent were male. They underwent 6 monthly scans and at the initial scan 15 lung cancers (0.43%) were identified, of which 14 were Stage I, with a mean tumor diameter of 16 mm. However, a total of 11.5% of CT scans were positive, requiring further assessment. The study has been updated to assess the incidence of lung cancers on the six monthly follow-up scans (22). A total of 1,180 participants were given two or more examinations, for a total of 7,891 scans. Of these, 721 (9.1%) were positive by helical CT, three times the rate of chest X-ray, and 22 (0.28%) of these were found to have lung cancer with 18 (82%) being Stage IA. The lung cancer detection rate was lower for the additional screening rounds compared with the initial screen and the 5-year survival rate was 64.9% compared with 76.2% for the initial prevalence cancers.

2. Sone and coworkers (23) screened a low-risk Japanese population of unselected volunteers including smokers and nonsmokers aged 40 to 74 years who had already undergone annual chest fluorophotography and sputum cytology as part of a national screening program. A total of 3,967 people underwent fluorophotography and low-dose helical CT, and each was matched with two control subjects from the same population who underwent fluorophotography only. Smokers from both groups underwent a 72-hour sputum collection for cytology. Each CT was read by four radiologists. Of the 3,967 participants, 19 (0.48%) were diagnosed with histologically confirmed lung cancer. In only one was the tumor detected by fluorophotography. Eight had abnormalities on a conventional chest radiograph. High-resolution CT missed one central tumor that was detected by sputum cytology. Of the 19 cancers, 16 were Stage I and 3 were Stage IV; 12 of the 19 were peripheral adenocarcinomas. Despite the relatively large number screened the pick-up rate was relatively low, and there was no difference in pick-up rates between smokers and nonsmokers. Also, to find 16 resectable cancers, 223 participants were examined further by chest radiography and high-resolution CT, and some by transbronchial biopsy; 204 showed nothing wrong. This was, however, a lower risk population.

3. The study by Henschke and coworkers (24) chose a higher risk population. The Early Lung Cancer Action Project screened 1,000 symptom-free volunteers who were 60 years of age or older, had a smoking history of at least 10 pack-years (in fact, a median of 45 pack-years), and were deemed fit for thoracotomy and a life expectancy of at least 5 years. Each participant underwent chest radiography and low-dose helical CT. There were specific recommendations for the interpretation and further investigation of noncalcified pulmonary nodules. At the initial screening, CT identified 233 individuals with noncalcified pulmonary nodules, compared with 68 seen on the chest X-ray. All 233 then underwent high-resolution CT scans and biopsy samples from 28 subjects confirmed malignancy in 27, of which 18 were adenocarcinomas; there were no small cell tumors. Stage I tumors made up 23 of the 27 discovered, of which only 4 were visible on chest radiography and 26 were resectable. The prevalence of lung cancer found by CT was 2.7%, four times that of chest radiography, and the highest of all the prevalence studies reported to date; a reflection on the choice of population screened.

4. The University of Münster (Münster, Germany) has to date screened by annual CT 817 subjects who are over 40 years of age with a smoking history of at least 20 pack-years. In 11 subjects 12 cases of lung cancer (1.3%) were found, of which only 7 (58.3%) were Stage I. Three lesions that were investigated invasively were found to be benign (25).

5. Another study from the Mayo Clinic enrolled 1,520 individuals, aged 50 years or older, with a smoking history of 20 pack-years or more (26). All subjects agreed to undergo a prevalence CT scan and three annual incidence scans. The initial prevalence screen identified 22 cases of lung cancer, and the first incidence screen of 1,464 of the original population discovered an additional 3 tumors. Cell types were as follows: squamous, 6; adenocarcinoma, 15; large cell, 1; and small cell, 3. Twenty-two patients underwent curative resection and 7 benign nodules were resected. There were 13 postsurgical Stage IA patients (60%). A cause of concern was the high rate of detection of noncalcified benign nodules: 2,244 among 1,000 participants. A total of 2,053 were present in the prevalence scan. On the first annual incidence scan, 195 had resolved, 36 had been removed (more than 1 nodule was removed in some patients), 86 had grown, and 79 had become smaller; 1,657 were stable. Thus, about 98% of nodules are false-positive findings, which means, assuming the 13% incidence rate in this study, almost all subjects could have at least one false-positive screening after a few years, with considerable implications for resources and patient management.

These studies are all hypothesis generating, but it is too early to know whether detecting tumors that are in general smaller than when discovered on a chest radiograph will decrease mortality. All these studies have the in-built problems of lead time bias, length time bias, and overdiagnosis bias (27). Only large randomized controlled trials (RCTs) with a follow-up of 10 years or more and rigorous use of all-cause mortality as an end point (17) will answer this fundamental question. In addition to the prevalence data now available, the incidence data from the current uncontrolled studies will give valuable information as to how many of the smaller nodules (less than 10 mm in diameter) were, in fact, tumors and not identified as such during the initial CT screen. Although identifying nodules 10 mm in size or smaller gives a yield of cancers smaller in size than those discovered by conventional chest X-rays, these tumors will have undergone 25 to 30 volume doublings and will have a considerable propensity to form metastases (28). Furthermore, there are data to suggest that the relationship between tumor size, survival, and stage at presentation is not clear cut. One study of 510 patients found no statistical relationship between tumors of less than 3 cm and survival; patients with 3-cm masses had the same outcome as those with 1-cm nodules (29). In a related study of 620 patients there was no relationship between size of the primary tumor and stage at presentation. Patients with a 1-cm tumor had a similar stage distribution as those with 2- to 3-cm masses (30). Thus the biological behavior of tumors is variable and a fundamental part of the issue of long-term outcome.

There is growing pressure to include low-dose helical CT in the armamentarium directed at finding lung cancer for good emotive (31) but not yet evidence-based reasons. Much work still needs to be done. The larger prevalence studies have been performed in countries where peripheral adenocarcinomas are commoner—the United States and Japan. This appears not to be the case in Europe and care must be taken when advocating a technique such as this more widely. The choice of population to screen will have a major effect on the prevalence of tumors found, as already clearly demonstrated in the data accumulated so far. Age, sex, smoking history, and the presence of airway obstruction are the major risk factors for the development of lung cancer.

The issue of false-positive scans will need to be addressed. In the Japanese and Lung Cancer Action Project studies there were large numbers of subjects with noncalcified pulmonary nodules: 233 of the 1,000 in the Lung Cancer Action Project (24) and 66% in the Mayo study (26). The anxiety generated, the potential for overinvestigation, and the radiologic exposure these individuals receive suggest a need for further thought.

It is also worth noting that in clinical practice, most lung cancers occur centrally and are diagnosed by bronchoscopy. These tumors hardly feature in the CT screening studies; only two central tumors were discovered in the Lung Cancer Action Project screen (24) and one in the study by Sone and coworkers, and that tumor was found by cytology, not CT (23). It would appear that central lung cancers are too aggressive to remain occult and produce symptoms leading to diagnosis before or between screening tests because of their situation in major airways. They behave in an entirely different way than intrapulmonary "nodule" or peripheral cancer.

What of the cost in terms of machine time, scan interpretation, and resultant action? Attempts have been made to analyze the cost-effectiveness of screening for lung cancer, but such models make enormous assumptions and are probably premature (32). A proper screening program will require dedicated CT scanners, which may need to be mobile. In many countries there is already an unacceptable waiting time for staging CTs in patients known or suspected to have lung cancer, and the additional burden of

screening is not possible. Once hundreds of scans are generated by screening, radiographers will have to be trained to report them and show only abnormal scans to radiologists for practical time reasons. Inevitably, further high-resolution CT scans will have to be performed on subjects with abnormalities and many will then require biopsies. Many will also need regular follow-up high-resolution scans for several years. The costs and logistics and possible long-term effects of the investigative irradiation are considerable.

There is therefore no sensible alternative to embarking on carefully constructed RCTs in defined populations of sufficient numbers, members of which are followed for long enough to provide a clear answer about the potential of CT screening. Additional problems will occur if the technology of imaging moves ahead so fast that improvements will have to be incorporated into these prospective studies. For example, three-dimensional volumetric analysis of a nodule is already available and is more sensitive for showing size change than simple CT (33). Finally, will any control population accept an annual chest X-ray, or perhaps no screening chest X-ray, while being deprived of a chance for CT screening?

Biological Screening Tools

Biological screening tools are still in development and remain the subject of research. One surface marker for early detection of lung cancer is the heterogeneous nuclear ribonucleoprotein A2/B1, which is upregulated on premalignant bronchial epithelial cells. In reassessing sputum archived from the Johns Hopkins screening study, overexpression of A2/B1 was a more sensitive marker of early preinvasive malignancy than normal cytologic screening. Features of malignancy were identifiable 1 year before the conventional cytologic examination showed abnormalities, and before the tumor became visible by chest radiography (34, 35). Similar encouraging results have been shown in prospective trials of Chinese tin miners (36), North American patients with lung cancer who had undergone resection of their primary tumor but were at high risk of recurrent disease (35, 37), and UK patients under investigation for lung cancer (38).

Mao and coworkers (39) looked at early chromosomal and genetic alterations in lung epithelial cells and found that point mutations in the *p53* and K-*ras* genes in sputum samples preceded the clinical diagnosis of lung cancer in one case by more than 1 year. Other groups have identified areas of genomic instability that cause microsatellite alterations that can act as clonal markers of early malignant disease (40).

STAGING TESTS: AN UPDATE

It is beyond the remit of a single review to comprehensively summarize the current lung cancer staging literature, but newer techniques are becoming available and these, together with basic assessment of the patient, are discussed.

Who Sees the Patient?

As the average age of presentation for lung cancer is increasing, this may affect who the patient is referred to (e.g., a care of the elderly physician) and how aggressive the treatment is. Brown and coworkers (41) assessed 563 cases of lung cancer diagnosed in a 30-month period around Southend, England. Two hundred and forty (43%) were over 70 years of age. The incidence of lung cancer in the general population was 69 per 100,000, but in men over 75 years of age the incidence was 751 per 100,000. For all patients, the active treatment rate was 49% (surgery, radiotherapy, chemotherapy), but for patients not reviewed by a chest physician (n = 86) it was only 21%. There were large differences in initial treatment between age groups. For patients

with NSCLC reviewed by a chest physician, surgery was performed in 18% of those under 65 years of age, in 12% of those in the 65- to 74-year age group, and in 2% in those over 75 years of age. For patients with SCLC reviewed by a chest physician, 79% of those under 65, 64% of those in the 64- to 75-year age group, and 41% of patients over 75 received chemotherapy. If no histologic diagnosis was made, 37% of patients under 75 and only 5.4% of those over 75 received any treatment. Patients not reviewed by a chest physician were less likely to obtain a histologic diagnosis.

A similar review of the referral and treatment practice in a city in Yorkshire, England also found that almost half of patients with newly diagnosed lung cancer were not sent to a respiratory physician, and the treatment rates for surgery, radiotherapy, and chemotherapy for those patients were approximately half the rates for patients seen by a respiratory physician (42). Both studies reinforced the UK National Cancer Plan to identify a respiratory physician with an interest in lung cancer in every hospital to organize the care for patients with newly diagnosed lung cancer. It is probable that in an aging population referral patterns in other countries will be similar to those in the UK, with no exclusive referral pattern to a respiratory physician.

Computerized Tomography of the Chest

Computed tomography of the chest is important both in the diagnosis and staging of lung cancer. As a diagnostic tool it is a valuable adjunct to bronchoscopy. The yield at bronchoscopy is higher if CT shows a bronchus extending to the tumor (60 versus 25%) (43, 44). The probability that a lesion considered accessible to bronchoscopy on a chest X-ray can actually be diagnosed in this way is not easy to ascertain (45). A UK multicenter prospective study of 1,660 consecutive cases investigated by fiberoptic bronchoscopy because of a prior likelihood of lung cancer found definite evidence of tumor in only 57% (46). In a further 20%, appearances were suspicious; thus, in 20% of these tests, the investigation was unhelpful. Only 15% of these patients had a prior CT and whether this was of use to the bronchoscopist is not known.

Another study (47) suggests there are advantages if CT precedes bronchoscopy and the information from CT is used by the bronchoscopist. Costs were not greater, as the number of invasive tests was reduced. Of 171 patients suspected of having endobronchial cancer, 90 had a CT performed and reviewed before bronchoscopy. Six needed no further investigation because the CT was either normal, or consistent with benign disease or with widespread metastatic disease. Of the remainder, fiberoptic bronchoscopy was diagnostic in 50 of 68 (73%) compared with 44 of 81 patients (58%) who had a bronchoscopy first. Overall, a positive diagnosis was made after a single invasive test in 76% of the group having a CT first, and in 54% of the group that underwent bronchoscopy first. Only 7 of the CT-first group needed more than one invasive investigation, compared with 15 patients (18%) of the fiberoptic bronchoscopy-first group. The additional cost of a spiral CT in each patient was offset by the need for fewer invasive tests, even though they were more expensive. Because the majority of patients with lung cancer have a CT during their workup, it may be best done before fiberoptic bronchoscopy.

The spiral CT, using a special staging technique, is the mainstay of staging in lung cancer. This involves an automated bolus injection of contrast 20–30 seconds before the scanning is initiated. This time interval allows optimal enhancement of the mediastinal blood vessels. A maximum slice thickness of 5 mm is used to prevent errors from partial volume effects. The new multislice CT systems allow the whole thorax to be scanned with 3-mm slices during a single breath hold.

Despite advances in CT scanning technology, there remain important limitations for its use in staging, with preoperative predictions differing from operative staging in 35–45% of cases, with patients being both over- and understaged (48, 49). CT staging remains unsatisfactory for detecting hilar (N1) and mediastinal (N2 and N3) lymph node metastases, and for chest wall involvement (T3) or mediastinal invasion (T4), in which sensitivity and specificity can be less than 65% (50–53). These are critical areas that may make the difference between surgical and nonsurgical management decisions. One development has been single-photon emission CT in which technetium-99m-labeled tetrofosmin is taken up by lung cancers. In one study of 34 patients with lung cancer, CT when combined with single-photon emission CT gave a sensitivity of 94.7% and a specificity of 93.3% for the detection of mediastinal metastases; these levels of sensitivity and specificity were greater than those achieved with either technique alone (54).

Dynamic expiratory CT scanning can be used to assess chest wall and mediastinal fixation by showing decreased mobility of the fixed tumor (55). Ultrasound may also be useful for chest wall assessment. In a series of 120 patients with contiguity between the tumor and the chest wall at CT but no definitive invasion (as diagnosed by bony erosion), 19 patients were judged to have invasive tumor on ultrasound with a sensitivity and specificity of 100 and 98%, respectively, when compared with operative findings (56). In the 1990s, many studies compared CT findings with the gold standard of mediastinoscopy or surgery. They showed that, regardless of the threshold size of lymph node chosen, CT findings in isolation could not be taken as clear evidence of malignant nodal involvement and about 20% of all nodes deemed malignant on CT criteria will be benign. Size alone cannot be an exclusion criterion and the clinician needs to prove by biopsy or resection that a node is indeed malignant. CT, however, continues to play an important and necessary part in the evaluation of patients with lung cancer, and its use is supported by the most recent American Thoracic Society/European Respiratory Society statement on pretreatment evaluation in NSCLC, in which CT is recommended for evaluation of mediastinal nodes in all patients with suspected NSCLC (57).

Magnetic Resonance Imaging

One of the most important questions when staging lung cancer is whether the tumor is resectable. Tumor-induced proliferation of connective tissue adjacent to the tumor may be interpreted as malignant on CT scan and the tumor consequently overstaged even with the new multislice scanners. In these situations, magnetic resonance imaging (MRI) has advantages over CT because of its multiplanar imaging and the large differences in intensity between tumor and soft tissue. MRI is superior to CT scanning in delineating the mediastinal fat plane, which makes it a powerful tool for assessing mediastinal invasion (58). Other areas in which MRI plays a role are in assessing invasion of the root of the neck, chest wall, vertebral bodies, and diaphragm (51, 59–62). MRI has no advantage over CT in the evaluation of enlarged lymph nodes except in patients with renal disease, for whom contrast is contraindicated (58, 63).

Positron Emission Tomography

Because of the limitations of CT and MRI, the search for better noninvasive techniques to identify malignant disease has intensified. Currently, 2-[^{18}F]fluoro-2-deoxy-D-glucose-based PET scanning (hereafter referred to as PET) is the most promising. PET can detect malignancy in focal pulmonary lesions of greater than 1 cm with a sensitivity of about 97% and a specificity of 78% (64). False-positive findings in the lung are seen in granulomatous disease and rheumatoid disease, with false negatives in

carcinoid, alveolar cell carcinoma, and lesions of less than 1 cm (65–68).

As well as having a role in the evaluation of parenchymal nodules, PET is also valuable for evaluation of the mediastinum. However, image resolution of the current PET scanners is only 4–8 mm and requires complementary CT. The precise anatomical information from CT adds to the metabolic map of PET and helps distinguish, for example, N1 from N2 disease and central tumors from enlarged lymph nodes. A total of 29 published studies that examined the suitability of PET for the staging of NSCLC were reviewed by Laking and Price (69). A meta-analysis confirmed that PET is significantly more accurate than CT for detection of nodal mediastinal metastases, with a sensitivity and specificity of 79 and 91%, respectively, for PET versus 60 and 77%, respectively, for CT (70). The usefulness of the extra information gained from PET is itself dependent on the initial CT scan, so that PET has a sensitivity and specificity of 74 and 96%, respectively, for detecting metastasis in normal-sized mediastinal lymph nodes compared with 95 and 76%, respectively, when these lymph nodes are enlarged (71). It is important to remember this when drawing up clinical protocols or considering individual patients. False-positive mediastinal nodal scans occur in sarcoid and tuberculosis and other infections.

Is PET sensitive and specific enough to replace mediastinoscopy and lymph node sampling before thoracotomy and prevent futile operations without denying surgery to appropriate candidates? Several studies have addressed this question. In one study of 100 patients, PET accurately staged NSCLC in 83% of cases compared with 65% by conventional imaging (thoracic CT, bone scintigraphy, and brain CT or MRI). PET identified 9 patients with metastases that were missed on conventional imaging whereas 10 patients thought to have metastases were shown not to by PET. PET was more sensitive than conventional imaging for bone, and adrenal metastases, but is inappropriate for the detection of brain metastases because of the high glucose uptake of the normal brain. The negative predictive value of PET for N2 disease was 96%, similar to that of mediastinoscopy, suggesting that patients with negative mediastinal PET could go straight to surgical resection of the primary tumor (72). In a comparison of PET with CT against the gold standard of mediastinal lymph node dissection in 102 patients with resectable NSLC (73), results were complicated by the high sensitivity (75%) and low specificity (66%) of CT scanning for detection of mediastinal metastases, but only PET results (91% sensitive and 86% specific) correlated with the histopathology of the mediastinal lymph nodes. PET altered the stage determined by conventional imaging in 62 patients (42 were upstaged and 20 were downstaged). However, PET was still wrong in 13 cases (conventional imaging was wrong in 32) and surgical staging was required for a definitive result (73). This emphasizes that no one with a positive PET scan should be denied surgery without positive histology (71). PET was actually of greatest value in 11 patients in whom distant metastases were found. However, in nine patients PET was falsely positive for distant metastases. In another study, treatment plans based on conventional staging were compared with those based on incorporation of PET. PET changed management for 40 of 153 patients (34 patients had their treatment changed from curative to palliative and 6 patients had their treatment changed from palliative to curative) and gave more accurate prognosis of individual patients (74).

More recently, an attempt has been made by a group in The Netherlands to see whether patients actually benefit if PET is incorporated into the workup, and to address this question treatment plans based on conventional staging were compared with those based on incorporation of PET. In this PLUS (*P*ET in *Lu*ng Cancer *S*taging) study 188 patients with NSCLC from 9 participating hospitals were randomized to conventional workup (CWU) or CWU plus PET. The primary outcome was the ability of PET to minimize futile thoracotomies. Eighteen patients in the CWU group and 32 in the CWU plus PET group did not have a thoracotomy. In the former group, 41% had a futile operation, as opposed to only 21% in the PET group (p < 0.003). Importantly, there was no decrease in justified surgery due to PET. Assessment of resectability by CT and PET was discordant in one-third of the cases, and PET was correct in two-thirds. PET was superior to CT in identifying the best mediastinoscopy site and in 10 cases only PET suggested the positive biopsy site. Overall one futile thoracotomy was avoided for every five PET scans (75).

Who should have a PET scan? Despite the expense of PET scanning and its limited availability, cost–benefit analyses of published data, in both the United States (76) and Europe (71), have shown that it is cost-effective to carry out total body PET in patients with a negative mediastinal CT and an apparently resectable tumor as the cost is balanced by a better selection of patients for surgery. Patients with a positive mediastinal CT and no clinical suggestion of metastatic disease should go straight to mediastinoscopy. However, these recommendations remain impractical until there is better access to PET scanners and radiologists to interpret them. Ideally, because of the high negative predictive value, PET scanning should be performed in all those with no evidence of metastatic disease on CT who are considered for surgery; and, failing this, definitely in those preoperative patients with suspicious N2/N3 disease on CT scan.

Endoscopic Biopsy Techniques

Transbronchial lymph node sampling, directed by PET and CT, performed via a flexible bronchoscope is less invasive than mediastinoscopy and may save time and money in skilled hands. However, the sensitivity is variable (50–89% that of mediastinoscopy), although this may increase with endobronchial ultrasound (EBUS) or CT guidance (77–79). EBUS has been used mainly to estimate the depth of tracheobronchial invasion, but there was preliminary evidence showing that this technique might be useful in the assessment of mediastinal and hilar metastases (80). In a more recent study, 37 patients with lung cancer underwent EBUS and CT scanning. EBUS was much better than CT for detecting abnormal hilar nodes of less than 1 cm, for resolving individual nodes from node masses, and for assessing invasion of the pulmonary artery. It appears that EBUS and CT may complement each other in the assessment of hilar and subcarinal (Level 7) lymphadenopathy. However, with only 16 patients with positive node involvement diagnosed surgically it is difficult to draw any statistical conclusion from the study (81).

Another technique that is becoming increasingly important in the sampling of mediastinal, but not hilar, lymph nodes is transesophageal lymph node sampling under endoscopic ultrasound guidance (EUS) (82). This has the added advantage of avoided contamination of lymph node samples with malignant cells from the bronchial tree.

EUS is a technique that has been in use for more than 10 years. It makes use of a modified endoscope with an ultrasound transducer at the tip and gives excellent views of the structures that lie adjacent to the gut lumen. EUS from the esophagus gives access to the subcarinal (Level 7), aortopulmonary (Level 5), and posterior (Levels 8 and 9) mediastinum and is able to resolve nodes as small as 3 mm. However, the views of the paratracheal and anterior mediastinal areas are limited by distortion caused by tracheal air. By using curved echo-endoscopes it is possible to perform fine needle aspiration (EUS-FNA) of abnormal subcarinal and aortopulmonary window nodes with negligible risk of infection or bleeding (83, 84). This had a sensi-

tivity of 96% for malignancy in lymph nodes when bronchoscopy had been unhelpful (85, 86). Silvestri and coworkers looked at 27 patients with known or suspected lung cancer who underwent CT scan and EUS-FNA. They showed that EUS-FNA improved the sensitivity of CT scanning and granted access to lymph nodes not reached at mediastinoscopy (79). Wallace and coworkers studied 121 patients with lung cancer, using EUS-FNA of abnormal nodes. Of these, 97 had enlarged mediastinal lymph nodes and EUS-FNA confirmed malignancy in 75 (77%). In addition, 10 of 24 (42%) patients with normal mediastinal lymph nodes on CT had Stage III or IV disease on EUS-FNA (84), suggesting that it might be an even more powerful staging tool than mediastinoscopy (87).

Only one study has directly compared mediastinoscopy (upper and anterior mediastinum) with EUS-FNA (subcarinal and posterior mediastinal lesions) and, although there were only a small number of patients, the suggestion is that the two techniques may prove complementary, with different lymph node stations targeted by the two techniques (88). More recently, Larsen and coworkers have looked at the effect of EUS-FNA on the management of 84 patients with mediastinal masses adjacent to the esophagus. Diagnosis was confirmed by thoracotomy, mediastinoscopy, or follow-up over at least 1 year. In 29 patients with known lung cancer who underwent mediastinal staging, EUS-FNA has a specificity of 100%, a sensitivity of 90%, a negative predictive value of 82%, and a positive predictive value of 100%. Similar figures applied for 50 patients with mediastinal masses but no obvious lung primary. The results from EUS-FNA provided a definite diagnosis and obviated the need for 28 mediastinoscopies and 18 thoracotomies. There were no complications from the procedure (89).

So, what is the role of EUS-FNA in patient management? Harewood and coworkers have used models based on the medical literature to look at cost minimization in the accurate staging of patients with NSCLC and enlarged (greater than 1 cm) subcarinal lymph nodes on CT scan. The lowest cost workup was by initial EUS-FNA provided that the probability of subcarinal lymph nodes metastases was greater than 24%, assuming a sensitivity for EUS-FNA higher than 76% (90), in keeping with other studies (91). EUS-FNA may prove as valuable as or more so than mediastinoscopy, and ideally is the investigation of choice for diagnostic evaluation of CT-suspicious lymph nodes at Levels 5, 7, 8, and 9. However, because of the requirement for expensive equipment and a skilled endoscopist, EUS-FNA is available only in a small number of institutions. In addition, the role of EUS-FNA in the evaluation of patients with apparently resectable lung cancers and normal mediastinal CT scans is unknown, but there is some evidence that it might identify some of the 10% of patients with N2/N3 disease who are not picked up by CT scan or mediastinoscopy. There may be some advantages over PET scanning, which has a false-positive rate of up to 13%, although the possibility of overstaging with EUS-FNA has not really been addressed.

The Search for Extrathoracic Metastasis

Current evidence suggests that, having established resectability of a primary lung tumor by the staging procedures described above, the clinician should search for metastatic disease only if there is an indication to do so. The preferred scans for picking up metastatic disease, in addition to the CT scan of the chest, are a CT or MRI with contrast of the brain and a technetium bone scan. The use of whole body PET scans for extrathoracic staging is still evolving, but current studies suggest it can identify noncerebral metastatic disease not detected by standard techniques in up to 20% of patients.

The presence of extrathoracic metastatic disease in NSCLC is dependent on the extent of intrathoracic involvement, that is, the worse the primary tumor and nodal involvement, the greater the likelihood of metastatic disease, whereas the incidence of silent metastases in Stage I disease is low (1%) (92, 93). Several studies, including two meta-analyses of the literature, have found distant metastases in only 2.5–5% of patients with potentially operable NSCLC despite normal clinical examination (94–97). The metastases most commonly affected brain, bone, liver, and adrenal glands in that order (95, 98). How best to identify these patients preoperatively and prevent a needless thoracotomy is not clear. The literature is divided, with some studies showing that screening all patients for extrathoracic metastases before thoracotomy is cost-effective (99) and others finding that this was not the case (92). It is now standard to include the adrenals and liver as part of a staging CT of the chest and upper abdomen (100).

Adrenals. The majority of unilateral adrenal masses in patients with lung cancer are benign but are difficult to distinguish from adrenal metastases (101, 102). A negative PET scan or MRI of the adrenals will exclude metastatic disease, but both tests have a high rate of false positives (102, 103). For this reason FNA should be performed on any suspicious adrenal masses (i.e., those of more than 2 cm or more or that are positive for PET or MRI) if this is the only obstacle to possible resection.

Brain. Metastases to the brain are more frequent when the primary tumor is greater than 3 cm (104) and more frequent for adenocarcinoma than for squamous cell carcinoma (94). Routine brain imaging in the absence of symptoms or clinical signs is not recommended as the pick-up of occult cerebral metastases is less than 3% (57), with a false-positive rate in one study of 11% (105). In a study of 114 patients staged by CT of the brain, thorax, and abdomen occult disease of the brain and abdomen was found in 15 patients, but in all but 3 cases (2 isolated abdominal metastases and 1 isolated brain metastasis) the CT scan of the thorax was sufficiently abnormal to demonstrate that the tumor was unresectable or to have prompted mediastinoscopy before thoracotomy (96). Colice and coworkers performed a cost analysis and concluded that, at current costs and given current available treatments, head CT should be reserved for those patients with abnormal neurologic symptoms and signs (106). High-dose gadolinium contrast-enhanced MRI (which is more sensitive than routine CT scanning for detecting brain metastases [107]) picked up occult cerebral metastases in 6 of 29 patients (17%) with lung tumors greater than 3 cm on CT scanning (104). There were no false-positive brain MRIs and no patient who had a negative MRI presented with cerebral metastases in the 12 months of follow-up. The preoperative detection of cerebral metastases altered treatment and follow-up for all patients, although surgery was not reconsidered for any patient in this study. This does suggest that in patients with primary tumors of greater than 3 cm, especially if these are adenocarcinomas or large cell, there may be an indication for MRI of the head as part of the staging procedure.

More recently, a multicenter, prospective randomized trial of 634 patients by the Canadian Oncology Group was designed to finally answer the question concerning whether to search for occult metastases in the asymptomatic patient with a resectable lung tumor and no clinical suggestion of extrathoracic spread (99). Although thoracotomy without recurrence occurred less often in patients who underwent full investigation (bone scintigraphy and CT of the head, thorax, and abdomen) as opposed to limited investigation (CT of the thorax with mediastinoscopy and other investigations as clinically indicated), the survival results were similar (99). In the meantime, we agree with the recommendations of Silvestri, that, before attempted resection, all patients should have a comprehensive clinical examination

TABLE 2. COMPARISON OF 1986 AND 1997 STAGE GROUPING OF TNM SUBSETS

International System for Staging Lung Cancer, 1986	TNM Subset*	International System for Staging Lung Cancer, 1997
0	Carcinoma *in situ*	0
I	T1N0M0	IA
	T2N0M0	IB
II	T1N1M0	IIA
	T2N1M0	IIB
	T3N0M0	
IIIA	T3N1M0 T1N2M0 T2N2M0 T3N2M0	IIIA
IIIB	T4N0M0 T4N1M0 T4N2M0 T1N3M0 T2N3M0 T3N3M0 T4N3M0	IIIB
IV	Any T, any N, M1	IV

Definition of abbreviations: M = metastasis; N = node; T = tumor.
* Staging is not relevant for occult carcinoma, designated TxN0M0.

and even the subtlest of abnormalities should be investigated (108). Asymptomatic patients with Stage I disease should not be investigated further, but a routine search for metastases is recommended in any patient with known or suspected N2 disease (108).

Refining of the Staging Classification in an Attempt to Increase Resectability

NSCLC is staged on the basis of the International System for Staging Lung Cancer. This system, in use since 1986, was modified in 1997 into 18 possible subsets that are grouped into 8 stages (including a Stage 0) that more accurately group patients with similar prognosis and treatment options (109). At the same time anatomic landmarks for 14 hilar, intrapulmonary, and mediastinal lymph node stations were designated for consistent lymph node mapping (110). In particular, it was hoped that a reclassification would emphasize the suitability of surgery for certain patients, remove some of the regional differences in treatments offered, and ultimately lead to increased patient survival.

What were the 1997 modifications and have they made a difference? The modifications included a regrouping of TNM (T, tumor; N, node; M, metastasis) subsets in Stages I, II, and IIIA (Table 2), some minor changes to the TNM classification to clarify satellite lesions, and recommendations for the classification of mediastinal, hilar, and intrapulmonary lymph nodes, combining the features described by the American Joint Committee on Cancer and the American Thoracic Society.

Stage I has been divided into IA and IB to reflect the different 5-year survivals of 67 and 57% for pathologic stage (pStage) I and pStage II, respectively (109), and as an impetus to focus attention on the need to improve survival of patients with Stage IB disease, among whom the 5-year survival is 46–57%. Stage II includes T1 (IIA) and T2 (IIB) tumors with spread to the peribronchial, lobar, and hilar lymph nodes (N1), and like Stage I patients these patients should be considered for surgery. T3N0M0 was moved from IIIA to IIB to reflect the better prognosis compared with other Stage III disease presentations, and its similar prognosis to that of T2N1M0. Stage IIIA now includes mainly patients with N2 disease. This group remains extremely

heterogeneous, with only a small minority considered resectable. In particular, there are differing prognoses for those patients with preoperatively diagnosed N2 disease (5-year survival of 9% for both pathologic [111] and clinically [112] diagnosed disease) as compared with "unforeseen" N2 disease (5-year survival of 24–34% [111, 112]).

Stages IIIB and IV, which are rarely considered resectable, are unchanged apart from the clarification of satellite lesions. Those satellite lesions in the same lobe are now T4 (Stage IIIB), and those that are ipsilateral and in a different lobe or contralateral are now M1 (Stage IV). Stage IV includes any patient with distant metastases; however, the demarcation for supraclavicular (N3; Stage IIIB) versus cervical nodal metastases (M1; Stage IV) remains imprecise and if there is any doubt the patient should be assigned the better prognostic stage. Tracheobronchial lymph nodes are designated as intrapulmonary hilar lymph nodes (N1) instead of mediastinal (N2). (However, if a lymph node can be sampled at mediastinoscopy without creating a pneumothorax then it should be designated N2.)

An extremely detailed single-institution staging analysis was made of 3,043 patients with primary carcinoma of the lung who underwent thoracotomy between 1961 and 1995. The aim of the study was to see how the new staging system stood up in practice (113). Patients were assigned a clinical stage (cStage) and a pathologic stage (with at least 100 patients in each stage) and were followed up for a mean of 116 months. All patients who underwent complete resections were staged by meticulous mediastinal dissection, rather than by mediastinal lymph node sampling. When survival curves were plotted for each pathologic stage against time, there were significant differences between the survival curves of all pathologic stages except for an overlap between pStage IB and pStage IIA. There was a much smaller difference between the survival curves for each clinical stage, emphasizing the superiority of accurate pathologic staging. The study was presented as an endorsement of the current staging with some recommendations: although patients designated as T3N0M0 had a good prognosis, those with tumors invading the chest wall, superior sulcus, diaphragm, and ribs had a poorer prognosis and should be reclassified as T4; patients with separate

tumor nodules in a different lobe had a better prognosis than other patients with M1 disease and should be reclassified.

However, Naruke and coworkers do not comment on the heterogeneity of Stage IIIA, which includes patients with N1 disease (5-year survival of 41.8%) and those with both bulky and "unforeseen" N2M0 disease (overall 5-year survival of 19.9%) (113). The survival rates of patients with T1N2 and T3N1 lung cancers are probably higher than those of patients with other subsets of Stage IIIA, but they are only considered as part of the larger groupings T1–2N2M0 and T3N1–2M0 and their better prognosis is masked (113). In two other prospective studies of 586 patients (114) and 2,361 patients (115), there was reasonable correlation between stage groupings and 5-year prognosis but again no significant difference in survival between Stage IB and IIA patients. There was again significant heterogeneity among those assigned to Stage IIIA, with 5-year survival spanning from 25 to 35% in patients with T3N1 disease (similar to Stage IIB survival of 27–33%) to 6–7% in those patients with T3N2 disease (114, 115), leading to the suggestion that T3N1M0 be moved to Stage IIB to reflect the better prognosis of this group (115).

Another point from the study by Naruke and coworkers (113) is that we are still failing some patients who have the best chance of a surgical cure: 21% of pStage IA and 29.2% of cStage IA do not live for 5 years. This suggests that anatomical staging is either too inaccurate or is not the whole answer and raises a question concerning whether some patients have particularly aggressive tumors that could be identified preoperatively. One study of 1,020 cases of pStage IA and IB lung cancer showed more prognostic significance if pStage I is divided into 4 groups depending on tumor size (0–2, 2.1–4, 4.1–6, and 6.1–8 cm), but even the group that does best has only a 63% 5-year survival (116). This has raised interest in prospective and retrospective studies to look at molecular genetic markers, growth factors, receptors, and host and tumor factors relating to cell proliferation and angiogenesis. For example, D'Amico and colleagues looked at a series of 408 patients who underwent resection for pStage I NSCLC and found a higher association of recurrence and death with four molecular markers: p53, Factor VIII, Erbb2, and CD44 (hazard ratio [HR], 1.4–1.68) (117). Molecular staging remains a research tool but undoubtedly will play a greater part in lung cancer management over the next 10–20 years, informing our treatment decisions.

Although much progress has been made, further refinement of the classification of lung cancer is inevitable, and this will require the meticulous standardized collection of staging and survival data from individual patients. In particular, the new guidelines will have to incorporate some of the new methods of investigation now available. Probably the greatest advance has been the development of metabolic staging using PET. This provides a move away from the strictly anatomical imaging used to stage lung cancer and promises to refine the selection of patients for resection; a promise that remains to be definitively proven. Another advance may be the molecular staging of lung cancer in an attempt to classify lung cancers not just by cell type, but on the basis of genetic make-up and biochemical behavior to account for the differences in metastatic potential and sensitivity to chemoradiation that different tumors show. How will we measure our success? Good staging should result in better treatment choices and ultimately increased survival, with better quality of life, and a reduction in futile thoracotomies, noncurative operations, and ineffective chemoradiotherapy.

ADVANCES IN RADIOTHERAPY IN NON–SMALL CELL LUNG CANCER

In general, there have been few advances in radiotherapy to improve the survival of patients with lung cancer. There is a probable dose–response effect for radical radiotherapy up to doses toward 70 grays (Gy), and standard doses can provide excellent palliation for some symptoms in patients with advanced disease. Various questions have been raised: can concurrent chemotherapy act synergistically with radiotherapy? Does the manner of dose administration matter (e.g., conventional daily doses versus accelerated regimens of more than one dose a day)? When part of a multimodal treatment, should radiotherapy be given concurrent with chemotherapy or sequentially? Most of these questions surround the use of radiotherapy in locally advanced inoperable Stage IIIA or Stage IIIB disease, but it also has been evaluated as an alternative to surgery and after successful resection (postoperative radiotherapy).

Radical Radiotherapy for Stage I and II Disease

There are patients who, although technically operable, either refuse surgery or are not medically fit. Such patients can be considered for radical radiotherapy with curative intent. However, there has been only one RCT, conducted between 1954 and 1958 by the UK Medical Research Council (MRC), to assess the value of radical radiotherapy as an alternative to resection (118). Fifty-eight patients were randomized to resection or radical radiotherapy; survival at 4 years was 23% for surgery and 7% for radiation. This was not a significant difference but became so when the analysis included only those with squamous cell cancer. Since then, a large number of nonrandomized studies, using a range of radiation doses, have reported their survival figures (119–125). All these studies suffer the disadvantage of having only clinical staging data; if staged surgically (at thoracotomy), there would be significant upstaging of patients as clinically occult N2/N3 disease was discovered. Also, these studies vary in patient selection and staging methods, for example, CT versus chest X-ray, but also with the extent of comorbid disease present.

Using a complete response (CR) as a prerequisite for long-term survival or cure, the CR rates ranged from 38 to 46% (120–122), but declined with increasing initial tumor size. The best results occur in tumors less than 4 cm in diameter, for which CR rates range from 48 to 52% and local relapse rates are lower, than for larger tumors with CR rates of up to 20% and higher local relapse rates (123, 126, 127). Overall, 5-year survival varies among these studies from 6% (118) to 32% (120). Whereas tumor size and radiation dose appear to be prognostically important variables, there seems to be no effect of age or histologic cell type on survival. It is possible that modern treatment with CT planning and conformal treatment, in which the shape of the radiation beam is molded to the tumor, may produce better results, but there are as yet no data.

Postoperative Radiotherapy

Postoperative radiotherapy (PORT) had been standard treatment after surgical resection of N2 disease. Its ability in moderate doses of 40–55 Gy to eradicate microscopic residual disease and reduce local recurrent rates is well established (128, 129). What has remained controversial is whether this improved local control leads to better overall survival. A meta-analysis of patients with any resectable stage tumor randomized to no further treatment after surgery or PORT was published in 1998 (130). The analysis of nine RCTs found a significant adverse effect of PORT on survival with an HR of 1.21 or a 20% relative increase in the risk of death. Whilst this has not been disputed for Stage I and II disease, the negative impact of radiotherapy tended to disappear when moving from Stage I to Stage III and from N0 to N2 disease. The possible benefits of radiotherapy may have been lost due to (by today's standards) poor radiation technique in many of these older trials conducted between 1965 and 1995.

The question, therefore, as to whether PORT has a role in Stage IIIA disease after resection is still not completely certain.

A study by Keller and coworkers (131) enrolled 488 patients who underwent resection of Stage II or Stage IIIA disease, and were then randomized to PORT alone (50.4 Gy) or PORT with four cycles of cisplatin and etoposide concurrent with 50.4 Gy. The median survival for patients undergoing PORT alone was 39 months, and the median survival for those receiving chemotherapy and radiotherapy was 38 months, that is, there was no additional advantage for chemotherapy.

Radical Radiotherapy for Stage IIIA and IIIB Disease

Stage III NSCLC comprises a large and heterogeneous group of patients, probably 30% of all new cases. In general, the 5-year survival with treatment does not exceed 5% and without mediastinal staging, it is often not possible to distinguish those with Stage IIIA disease and those with Stage IIIB disease. However, regarding outcome, this appears to make no or little difference (132) and the two groups can be combined. Most studies reporting treatment in RCTs for this group of locally advanced patients contain a mixture of patients with Stage IIIA or IIIB disease.

It is beyond the remit of this review to discuss the basic principles of irradiation, fractionation, and field size. However, prognosis after radical radiotherapy depends on initial tumor size and nodal status, although most studies report an overall 3-year survival of 2–20% and a median survival of 8–12 months (133–136). Better survival is reported for higher doses, for example, the 3-year survival was 6% with 40 Gy, 10% after 50 Gy, and 15% after 60 Gy given in daily fractions of 2 Gy. The higher dose regimens also provided better, more durable local control (137). Dose intensity can also be increased by three-dimensional conformal radiotherapy, which restricts the dose to the tumor while protecting normal tissues (138) and is the result of better imaging technology using CT and MRI (139). These techniques continue to be evaluated.

In addition to dose, studies have addressed the question of hyperfractionation (more than one dose per day). Hyperfractionation regimens use two or three fractions per day of 1–1.2 Gy separated by at least a 6-hour interval, while keeping the same total dose as the classic once-daily fraction regimens. This approach was originally investigated by the Radiation Therapy Oncology Group (RTOG). After a large Phase II trial to select the optimal radiation dose, the RTOG performed a three-armed trial: a daily schedule to 60 Gy, 69.6 Gy with two daily fractions each of 1.2 Gy, and a third arm of induction chemotherapy consisting of two cycles of cisplatin and vinblastine followed by 60 Gy in daily fractions for 6 weeks (140, 141). The 3-year survival rates were 6% after 60 Gy, 15% in the induction chemotherapy arm, and 13% after hyperfractionation. The results were not statistically significantly better for induction chemoradiation compared with radiation alone.

The CHART regimen (continuous hyperfractionated accelerated radiotherapy) was developed in the UK. Treatment is given three times a day as 1.5-Gy fractions for 12 days including weekends to a total of 54 Gy and was compared with conventional daily radiotherapy to the same total dose (142). Overall, in 563 randomized patients, CHART demonstrated a 9% improvement in survival at 2 years (20 to 29%) and this was even more marked for squamous cell tumors (82% of all cases), for which there was a 34% reduction in the relative risk of death and an absolute improvement in survival at 2 years from 19 to 33%. Although severe dysphagia occurred more commonly in the CHART group, it was transient and manageable. CHART has provided a significant step forward in the methodology of administering radiotherapy, but for logistic reasons, mainly the inability to provide radiographer expertise at weekends, CHARTWEL (CHART with WeekEnd Leave) is being examined with and without adjuvant chemotherapy. American groups utilizing versions of CHART have also eliminated weekend treatments, but deliver three fractions of irradiation per day as HART (hyperfractionated accelerated radiation therapy). An Eastern Cooperative Oncology Group (ECOG) feasibility study using this regimen obtained a median survival of 13 months with acceptable toxicity (143).

Palliative Radiotherapy

Radiotherapy can be effective at relieving local symptoms of lung cancer. Quality of life data from the British MRC randomized trials of 1 and 2 fractions of treatment versus more conventional treatment consisting of 10 or 13 fractions have shown improvement in local symptoms, including chest pain, cough, and breathlessness, in more than 50% of cases, with 90% of those having hemoptysis being controlled (144–146). Although palliative irradiation is of widespread use, there have been only a few RCTs addressing the question of dose, palliative effect, and survival (144–149). These showed that shorter schedules using one or two fractions of radiotherapy are just as effective at obtaining relief of local symptoms without detriment to survival time or an increase in toxicity relative to higher dose, short courses. The MRC studies (1991, 1992, and 1996) also included careful assessment of quality of life with daily diary cards, confirming good durability of palliation and minimal toxicity.

The most recent MRC palliation study (146) assessed patients with good performance status and compared 2 fractions, each separated by 1 week (total, 17 Gy), with 39 Gy given in 13 fractions. The study confirmed good palliation with a two-fraction regimen, but a small survival advantage for the higher dose regimen (3% at 2 years). This was not confirmed by an RTOG study, which showed no survival difference between 30 Gy in 10 fractions, 40 Gy in 20 fractions, and 40 Gy in 10 fractions (147).

Interventional Bronchoscopy and Brachytherapy

Smaller doses of radiotherapy can be used if delivered directly to the airway (endobronchial brachytherapy) and are particularly useful in those patients who have received close to the maximum safe dose of external beam radiotherapy, and in those with tumor localized to within or close to the airway lumen. Radical radiotherapy can also be delivered in this way. Endobronchial brachytherapy has been used in one form or another for at least 80 years with radium needles and cobalt pearls used commonly in the 1960s and 1970s to destroy local tumor in the upper airways. Iridium has now become the standard mode of delivery of irradiation via a catheter placed in the airway through a flexible bronchoscope under radiographic control. Iridium provides small-volume irradiation with a steep decrease in radiation isodoses within a few millimeters of the source axis. The target dose depends on the intent, with 10–15 Gy in 10 mm for palliation, and 20–25 Gy if cure is intended for a localized small lesion. The response to brachytherapy is slow, over 10 to 20 days, and appears to be safe in doses of 5 Gy over two to four sessions, even if radical radiotherapy has been given earlier. In fact, the commonest setting for brachytherapy is for local relapse after previous radical radiotherapy. Few controlled clinical data exist for trials of brachytherapy; for example, there is no standard indication for treatment or for evaluating its response, no standards for fractionation or dose calculation, and no recommended staging process to define the effective extent of the treatment. Most studies report their results retrospectively.

Brachytherapy seems to be used after endobronchial tumor clearance, but few studies have evaluated its benefit. One pro-

spective RCT of neodymium:yttrium–aluminum–garnet (Nd:YAG) laser alone versus laser plus brachytherapy reported an additional 7-month symptom-free interval with both treatments and a reduced need for further endoscopic interventions (150). As a palliative tool, brachytherapy seems impressive with hemoptysis being controlled after one treatment in 70% of sufferers, pneumonia in 57% and cough and dyspnea in 30%. The main complication is massive hemoptysis which can occur in up to 9% of cases in larger series (151, 152).

CHEMOTHERAPY FOR NON–SMALL CELL LUNG CANCER

As surgical resection or radical radiotherapy may cure only 10% of all patients with NSCLC, 90% will present with or develop advanced disease and ultimately die from their tumor. Although chemotherapy may be a logical approach, there is virtually no evidence that it can cure NSCLC. There is, however, increasing evidence that it can palliate and prolong life in some patients, but only for a few months. The monetary cost for this extension of life is high and increases with the development of newer, more expensive drugs, which may have some advantages in ease of administration and toxicity but only small gains in terms of prolonging median survival, with more patients alive at 1 year. A newer regimen, such as paclitaxel in advanced NSCLC, costs 12 times that of mitomycin, ifosfamide, and cisplatin (MIC) in the UK. It saves on inpatient administration time and may, in some studies, result in a greater number of patients being alive at 1 year. The cost effectiveness of these regimens is the subject of debate in the UK at present. The other costs of chemotherapy, that is, its toxicity and its potential detriment to quality of life, are even more important questions, the answers to which are only now beginning to emerge.

Chemotherapy has been evaluated as neoadjuvant and adjuvant treatment around surgery, neoadjuvant and adjuvant around radiotherapy, and as primary treatment for advanced inoperable disease.

Neoadjuvant Chemotherapy

A place for chemotherapy before surgery has been controversial for the last 10 years. There are two issues: first, what is the role for neoadjuvant chemotherapy in conventionally resectable patients, that is, those with Stage I or II disease (T1, T2, or T3, N0; T1, T2, or T3, N1) and also limited Stage IIIA disease, that is, unforeseen N2 disease with normal nodes at CT but microscopic N2 disease at mediastinoscopy? The second issue is whether chemotherapy can "debulk" more advanced disease,

for example, N2 nodes found on CT, T4 primary tumors, or N3 disease. These patients would not normally be considered for surgery and are treated by radical radiotherapy or chemotherapy–radiotherapy. However, if chemotherapy were a really effective treatment, could surgery follow chemotherapy and be more effective than radical radiotherapy? The answer to the first question is "possibly," and the answer to the second is not at all clear.

There are only five published RCTs of neoadjuvant chemotherapy versus surgery alone; three were negative (153–155) and two were positive (156, 157) (Table 3). A potential confounder in all these studies is the inconsistent addition of pre- and/or postoperative radiotherapy for some patients, usually if residual disease remained after resection.

Much of the data for the possible benefit of neoadjuvant chemotherapy is from Phase II trials, often with small numbers, and some trials use chemotherapy alone and others use both chemotherapy and radiotherapy preoperatively. The chemotherapy regimens vary, and the administration of radiotherapy also varies: preoperatively, intraoperatively, postoperatively, or not at all. Some studies accepted clinical staging and others documented only pathologic nodal staging.

Of the Phase II studies giving chemotherapy followed by surgery (158–162), four used mitomycin, vinblastine, and cisplatin (MVC); one used cisplatin and 5-fluorouracil, and one used vinblastine and cisplatin. Some of these studies also gave irradiation, usually postoperatively, but details are scanty. Response rates to chemotherapy varied from 51 to 78% and resection rates were high: 51–68%. The overall perioperative mortality ranged from 0 to 17% and median survival ranged from 12 to 20 months. About 25% of all resected patients had a subsequent local relapse. Of interest, in a UK study (162), 45% of potential patients refused to enter such a study design, refusing chemotherapy. No clinical or pathologic complete responses were obtained in those given neoadjuvant treatment.

A retrospective review of one institution's experience of the perioperative mortality for patients undergoing neoadjuvant chemotherapy and surgery (n = 76) compared with surgery alone (n = 259 patients) found no differences for mortality or morbidity based on clinical stage, postoperative stage, or extent of resection between these two groups of patients, which is reassuring (163).

There are other Phase II studies in which neoadjuvant radiotherapy was given with chemotherapy (164–167). In essence, the resection rates after the combination treatment were a little higher than for chemotherapy alone (52–76%), but the median survival rates (13–22 months) were no better.

TABLE 3. PHASE III RANDOMIZED STUDIES OF SURGERY WITH OR WITHOUT INDUCTION THERAPY IN RESECTABLE NON–SMALL CELL LUNG CANCER

Study (Ref.)	Stage	Chemotherapy	Radiotherapy	n	2- to 3-yr Survival (%)		p Value
					No CTX	CTX	
Pass and coworkers (153)	IIIA, N2 by biopsy	EC pre- and post-op	Post-op in no-CTX arm	28	21	46	NS
Yoneda and coworkers (154)	Clinical IIIA and IIIB	VdC pre-op	Concurrent with CTX	83	40	37	NS
Roth and coworkers (156)	II–IIIB, node biopsy not required	CyEC pre- and post-op	Post-op if residual disease	60	15	56	< 0.05
Rosell and coworkers (157)	IIIA (N2), node biopsy not required	MIC pre-op	Post-op both arms	60	0	30	< 0.05
Depierre and coworkers (155)	Clinical T2N0; Stage II, IIIA	MIC pre-op, post-op if objective response	Post-op if pT3 or pN2 both arms	355	41*	52*	NS

Definition of abbreviations: C = cisplatin; CTX = chemotherapy; Cy = cyclophosphamide; E = etoposide; I = ifosfamide; M = mitomycin; NS = not significant; pN2 = pathological N2; pre-op = preoperative; post-op = postoperative; pT3 = pathological T3; V = vinorelbine; Vd = vinblastine.

Adapted from Albain KS, Pass HI. Induction therapy for locally advanced NSCLC. In: Pass HI, Mitchell JB, Johnson DH, Turrisi AT, Minna JD, editors. Lung cancer. Baltimore, MD: Lippincott-Williams & Wilkins; 2000.

* Three-year survival.

The role of induction therapy has been addressed only in RCTs for early-stage or minimal N2 disease (negative CT of the mediastinum with either no or minimal N2 involvement at mediastinoscopy). These patients would be eligible for surgery alone, and have less bulky disease than those in the Phase II studies described above. The five studies are summarized in Table 3. The two positive studies by Roth and coworkers (156, 168) and Rosell and coworkers (157, 169) closed early because of disparity in survival between the two arms, a statistical hazard when applying early closure rules to small studies. However, the median survival differences have become smaller at 5 years (0 versus 17% in the study by Rosell and coworkers, and 15 versus 36% for Roth and coworkers), although still clearly favorable for the combined modality treatment. These studies have been criticized because the surgery-alone arms have fared badly, particularly in the study by Rosell and coworkers, in which there was a higher rate of tumor K-*ras* mutation and DNA aneuploidy, which are indicators of poor prognosis, than in the chemotherapy arm.

The much larger French study just published (155) included 355 patients with clinical Stage I (except T1N0), II, and IIIA disease randomized to surgery or two courses of MIC followed by surgery with an option for two further courses postoperatively. Patients with T3 and N2 disease received postoperative irradiation. A pathologic CR was seen in 11% of patients receiving neoadjuvant chemotherapy, but the survival data for the entire study were not significantly different at 3 years (p < 0.15; Table 3). There was no difference in the postoperative mortality rates: 6.7% in the chemotherapy arm and 4.5% in the surgery-only arm. The median survival was 37 months with neoadjuvant chemotherapy and 26 months with surgery alone. There was a significant survival advantage with neoadjuvant chemotherapy for patients with N0 and N1 disease, but not for those with N2 disease. It is suggestive, therefore, that there may be an added advantage for chemotherapy for survival with Stage I and II NSCLC. However, there was no evidence of added benefit with chemotherapy for Stage IIIA disease.

Thus, valuable information is emerging to define the role of neoadjuvant chemotherapy in patients with resectable disease. This population of NSCLC patients includes those most likely to respond to chemotherapy (good performance status, small-volume disease, and normal biochemical values) and, clearly, a small percentage improvement in overall survival data as a result of adding chemotherapy to surgery would affect a large number of patients with this common disease and would be an important step forward.

There are other studies in progress to assess this question. The UK MRC LU22 study is a pragmatic study of randomization to neoadjuvant chemotherapy, which is open to any patients deemed operable. However, patient refusal was high in a pilot feasibility study (162) and some surgeons are reluctant to enter patients because of the risks of tumor progression during chemotherapy and belief that there are risks of increased perioperative morbidity, making recruitment slow.

The other question, concerning whether neoadjuvant treatment is of value in downstaging locally advanced inoperable disease, appears more difficult to resolve. RCTs are in progress in which patients with bulky N2 disease, after induction chemotherapy or chemotherapy–radiotherapy, are randomized to surgery or completion radiotherapy or radical radiotherapy. These studies hope to recruit about 500 patients each and are progressing slowly.

Although neoadjuvant chemotherapy appears to be widely practiced outside clinical trials in some countries, the data for improved survival are more tenuous than for almost any other treatment policy in the management of lung cancer, and these studies appear to have particular difficulty in recruiting patients.

Most of the patients in the earlier studies, particularly the Phase II studies, would have been fitter, more motivated, often younger, with minimal comorbidity compared with the average patient currently undergoing routine resection for lung cancer. We may never have a clear picture of the real value of neoadjuvant treatment, or for which cell type or disease stage it may have a clear-cut benefit compared with surgery alone.

Adjuvant Chemotherapy and Surgery

The place of chemotherapy after surgery is likely to emerge clearly within the next 2 to 3 years. In 1995, the NSCLC Collaborative Group meta-analysis (170) reported 14 trials (4,357 patients) in which patients were randomized to receive or not receive chemotherapy after surgery. Five trials used long-term alkylating agents and showed a significant disadvantage for the addition of chemotherapy (HR, 1.15; confidence interval [CI], 1.04–1.27). Eight studies incorporated cisplatin, at a relatively low dose (40–80 mg/m^2). The HR for the eight cisplatin-containing regimens was 0.87 (CI, 0.74–1.02) and the absolute benefit for chemotherapy was 3% at 2 years and 5% at 5 years. The meta-analysis did not derive a significant advantage for the addition of chemotherapy after surgery (p < 0.08) and, therefore, several studies are now in progress, or have recently completed, that will be expected to answer this question, either as a single study or, more probably, as a new meta-analysis. These studies include the International Adjuvant Lung Cancer Trial (IALT), which randomizes completely resected patients to three or four cycles of cisplatin-based chemotherapy after surgery, or to no further treatment; the Adjuvant Lung Project, Italy, which also randomizes completely resected patients to cisplatin, mitomycin, and vindesine for three cycles or to control. The National Cancer Institute of Canada is randomizing patients with completely resected Stage IB and II disease to observation or treatment with cisplatin and vinorelbine. The North American Cancer and Leukemia Group B is using carboplatin plus paclitaxel versus control in completely resected Stage IB NSCLC. The Big Lung Trial in the UK will contribute about 400 patients randomized to control or to one of four cisplatin-containing regimens after surgery. Together, these studies will accrue in excess of 5,000 patients and should clarify whether the precise role of adjuvant chemotherapy is after surgery in NSCLC.

Chemotherapy and Radiotherapy in Locally Advanced Disease

With the lack of any clear advantage for adjuvant chemotherapy or PORT in resected N2 lung cancer, the possible benefits of combining chemotherapy with radiotherapy after resection have been studied. The logic is that radiotherapy decreases local rates of recurrence and chemotherapy may both add to this and treat distant occult disease. There have been four randomized controlled trials of surgery plus adjuvant chemotherapy–irradiation versus surgery and radiation alone (131, 171–173).

All these studies failed to show an advantage in overall survival, with the most recent failing to demonstrate any improvement in disease-free survival or overall survival with the addition of chemotherapy to radiotherapy (131).

The median survival of patients with locally advanced, inoperable NSCLC after radical radiotherapy is about 12 months. Both local and distant recurrence rates are high, explaining the logic of adding chemotherapy to radiotherapy to treat not only the primary tumor but distant micrometastatic disease as well. There have been many studies addressing this issue (174–180), with either no benefit or a small benefit for the combined treatment. The meta-analysis by the NSCLC Collaborative Group of individual data from all 22 RCTs in which patients were randomized to radiation alone or chemotherapy and radiotherapy (170) included 3,033 patients. There were two groups: older studies using

long-term alkylating agents and those using modern cisplatin-based chemotherapy (1,780 patients). The HR for those with alkylating agents was 1.02 (CI, 0.86–1.20), indicating no benefit. However, for cisplatin-based regimens, the HR was 0.87 (CI, 0.79–0.96), giving an estimated 4% benefit at 2 years for the multitreatment regimens. However, the long-term effects on cure rates are less obvious. The final results of the RTOG three-armed study reported above (140, 141) have been published (181). This now shows that the arm randomized to two courses of cisplatin and vinblastine followed by 60 Gy of daily radiotherapy at 2 Gy per day had a statistically longer median survival (MS; 13.7 months) and 5-year survival (8%) than the arm receiving 69.6 Gy at 1.2 Gy given twice daily (12-month MS, and a 6% 5-year survival) or the arm receiving 60 Gy alone, given at 2 Gy per day (11.4-month MS and 5% 5-year survival). These differences are small, but evidence suggests the administration of chemotherapy before radiotherapy does confer a small survival advantage. However, different studies have differing radiation doses, field sizes, fractionation details, and staging tests, making it difficult to compare the data.

Concurrent chemotherapy: radiation. Another question concerns the timing of radiation in relation to chemotherapy. The studies described above all gave chemotherapy before irradiation (i.e., sequential chemoirradiation). A European Organisation for Research and Treatment of Cancer (EORTC) three-arm study compared split-course radiotherapy concurrent with daily or weekly cisplatin versus radiotherapy alone (136). There was no advantage for the weekly chemotherapy plus radiotherapy arm. Furuse and coworkers (182) compared chemotherapy (mitomycin, vindesine, and cisplatin) given concurrently with radiotherapy versus chemotherapy followed by radiotherapy (56 Gy). The 320 patients were randomized and the median survival was significantly better for concurrent radiotherapy and chemotherapy (MS, 16.5 months) compared with chemotherapy before radiotherapy (MS, 13.3 months). The 3- and 5-year survival rates were, respectively, 22 and 16% for concurrent therapy and 15 and 9% for sequential therapy. Myelosuppression was significantly greater for the concurrently treated patients.

More studies are needed and the newer chemotherapy agents are being assessed alone or in combination with a platinum drug, for example, induction carboplatin with paclitaxel followed by weekly doses with concurrent radiation in a Phase II trial. This yielded a good response rate of 55% in 38 patients and acceptable toxicity (183).

However, large Phase III trials will be required to define the role and timing for these agents in the treatment of unresectable Stage IIIA (N2) disease.

Locally advanced Stage IIIB disease. Stage IIIB includes patients with T4, any N, N0 and any T, and N3M0 disease. Surgery may be indicated only for selected T4N0M0 subjects. Patients with unresectable disease and good performance status may be eligible for radical radiotherapy or for chemoirradiation trials and strategies.

Most of the adjuvant trials of radiotherapy with or without chemotherapy have included both Stage IIIA and IIIB patients. Results for the patients with Stage IIIB disease have not been analyzed separately. As the data from some Phase III trials and the NSCLC Collaborative Group meta-analysis (170) showed a small advantage in survival for adjuvant chemotherapy, this is recommended for patients with Stage IIIB disease without pleural effusions, performance status 0 or 1, and no weight loss.

What evidence there is suggests that these fitter patients with advanced disease can be incorporated into the same strategies for treating bulky unresectable Stage IIIA cancers, although there is no separate analysis of outcomes of these two disease stage groups.

Chemotherapy in Advanced Disease

Approximately 60% of patients of NSCLC present with Stage IIIB or IV (i.e., advanced) disease. They have a median survival of 4 to 6 months untreated and 10 to 15% will remain alive at 1 year (170). Early studies of single-agent chemotherapy and combinations of predominantly alkylating agents showed little benefit, but meta-analyses reported in the mid-1990s suggested a small but definite benefit with cisplatin-containing regimens compared with best supportive care (BSC) alone. The most comprehensive of these analyses was by the NSCLC Collaborative Group (170), which showed, in a total of 778 patients in RCTs between BSC or cisplatin-containing chemotherapy, an improvement in median survival from 17 weeks with BSC to 24 weeks with chemotherapy and a 10% improvement in survival at 1 year. These advantages are clearly modest, as the gain of 7 weeks' median survival is less than the duration of the courses of chemotherapy administered, and patients are exposed to the potentially toxic effects of therapy. A major criticism by the authors of the meta-analysis was that most of the RCTs contained little or no quality of life data. Clearly, if a disease cannot be cured by a particular treatment, the potential benefits in terms of quality of life have to outweigh direct toxic effects and also be reasonably cost-effective.

Since the meta-analysis of 1995, further studies of chemotherapy versus BSC have been published. Cullen and coworkers compared four courses of mitomycin (6 mg/m^2), ifosfamide (3 g/m^2), and cisplatin (50 mg/m^2) (MIC) with BSC in 351 patients and showed a median survival of 6.7 months with chemotherapy versus 4.8 months with BSC, with 25 and 17% alive, respectively, at 1 year (178). Quality of life was assessed in a subgroup of 109 patients (67 from the MIC arm and 42 from the BSC arm) and showed an overall improvement in symptom scores between the two time points measured at 0 and 6 weeks.

Another large study (184) compared BSC with ifosfamide (3 g/m^2), epirubicin (60 mg/m^2), and cisplatin (60 mg/m^2) (IEC) or mitomycin (8 mg/m^2), cisplatin (100 mg/m^2), and vinblastine (4 mg/m^2) (MVC) on Days 1 and 15. Patients received two to six courses of chemotherapy, provided they did not develop disease progression. Two hundred and eighty-seven patients were randomized and the median survivals were 4.1 months for BSC, 5.9 months for IEC, and 8.1 months for MVC with 1-year survivals of 13, 30, and 39%, respectively. Quality of life was assessed by Karnofsky Performance Scale, and modified Functional Living Index—Cancer (T-FLIC) and modified Quality of Life—Index (T-QLI) whereas Cullen and coworkers used the EORTC QLC-LC13 questionnaire and derived a total score. Thongprasert and coworkers assessed quality of life at entry, at 2 months, and 2 months after stopping chemotherapy or at 6 months after entering the BSC arm and showed improvement in quality of life at all three interviews in the chemotherapy arm only (184).

Anderson and coworkers (185) compared single-agent gemcitabine with BSC and found no survival difference, but better quality of life on the active arm.

A study of vinorelbine versus BSC in elderly patients (186) randomized 161 patients aged over 70 years and achieved a response rate of 19.7% and a better median survival of 28 weeks versus 21 weeks with BSC. One-year survivals were 32 and 14%, respectively.

Finally, another single-agent study compared doxetaxel and BSC with BSC alone in 270 patients under the age of 75 years. The randomization was to doxetaxel (100 mg/m^2) every 3 weeks and the response rate was 20%, with a median survival of 26 weeks for the treatment arm and 25 weeks for BSC (p = 0.026), that is, significant but clinically small. However, 1- and 2-year

survivals were better on the active arm: 25 versus 16% and 12 versus 0%, respectively (187).

These studies, briefly detailed above, do show an undoubtedly better median survival and 1-year survivorship for active treatment and, where available, an improvement in some measures of quality of life. The latter is still difficult to quantify and remains "soft" data. Most studies have taken patient subsets for quality of life analysis, used different measures with no agreed criteria for reporting, and, because of the attrition of the disease itself, the numbers returning questionnaires fall by 30–50% by 6 to 12 weeks, making the data more difficult to interpret. Furthermore, there is no agreement as to the standardization of the best time points to collect data during a study and it also makes a difference, depending on who is assessing patient symptoms (188).

Most studies show that, if qualify of life is to improve, it does so in most patients after two courses of chemotherapy (189) and worsens after prolongation of treatment. In a comparison of three courses with six courses of MVC, Smith and coworkers (190) showed significant increases in fatigue and adverse trends in chemotherapy-related side effects in those patients who continued beyond three courses of chemotherapy.

Furthermore, chemotherapy is not, in general, a popular treatment. In our own study of chemotherapy and BSC versus BSC alone (the Big Lung Trial; our unpublished data), the commonest reason given by patients refusing to enter the study was the desire not to receive chemotherapy (33% of those giving a reason for not entering) compared with 4% who did not enter because they wanted chemotherapy (191). Another enquiry into patient choice was made by Silvestri and coworkers (192): they asked patients who had already received six courses of chemotherapy whether they would have refused chemotherapy if they had known the treatment offered only a 3-month prolongation of survival; 68% said they would have refused chemotherapy, but they would have chosen it if it would definitely improve their quality of life.

It is certainly the authors' belief that, although chemotherapy does confer a survival advantage to some patients with NSCLC, this effect is in the order of 3 months, with poorly reproducible quality of life data. The London Lung Cancer Group has just completed the Big Lung Trial, a multicenter UK pragmatic study including 1,400 patients who are eligible for surgery, radical radiotherapy or have advanced disease, and are randomized to receive or not receive three courses of cisplatin-based chemotherapy in addition to their primary treatment. In the case of those with advanced disease, the randomization is to chemotherapy and BSC versus BSC alone. At closure, more than 700 patients with advanced disease have been randomized to this part of the study and 280 are in a quality of life study, using daily diary cards during the chemotherapy period or for 9 weeks during BSC, and the EORTC QLC-LC13 questionnaire is completed every 3 weeks for 6 months. It is hoped that this large study will clarify some of the issues regarding quality of life and survival in NSCLC.

Of course, not all patients with advanced disease will benefit from chemotherapy. Disease stage and performance status are the most important prognostic factors at presentation. Those patients most likely to respond to chemotherapy and tolerate side effects well are those with a good performance status, female sex, a single metastatic site, normal calcium and serum lactate dehydrogenase, hemoglobin at more than 11 g/dl, and the use of cisplatin chemotherapy (193). Of these, performance status is the most important factor, and of other variables analyzed, a poor prognosis is conferred if there are subcutaneous metastases, bone marrow infiltration, thrombocytosis, and non-large cell histology (194, 195). Most of the published trials of chemotherapy for Stage IIIB and Stage IV disease have been confined to perfor-

mance status (PS) ECOG 0–2, as poor performance status correlates with early death and a risk of severe toxicity, and these patients do badly (196). In a study of four more modern chemotherapy regimens for advanced NSCLC, an interim analysis showed that patients with PS 2 fared so badly that entry was limited to patients with PS 0 and 1 (197).

Newer Chemotherapy Combinations

At the time of the NSCLC meta-analysis (1995), the median survival of patients with advanced disease treated by chemotherapy was 23 to 35 weeks (5.75–8.75 months), with about 30% of patients alive at 1 year compared with BSC (11–26 weeks, or 2.75–6.5 months) and less than 20% alive at 1 year.

During the last 5 years, several new drugs have been evaluated including paclitaxel, doxetaxel, gemcitabine, vinorelbine, and tirapazimine. These drugs are almost always given with a platin, either cisplatin or carboplatin, the latter seeming as effective as cisplatin and, although more myelotoxic, is less oto- and nephrotoxic and needs no intravenous hydration.

The place of these agents has been reviewed extensively in textbooks and review articles. However, during the last 18 months, several large Phase III studies have been published and are summarized in Table 4.

All studies summarized in Table 4 are Phase III studies including large numbers of patients, looking in the main at the effect of the new agents, usually in combination with a platin drug.

Cardenal and coworkers (198) assessed the effects of gemcitabine with cisplatin compared with a standard regimen of cisplatin and etoposide (CE). Gemcitabine has consistently shown activity as a single agent in Phase II studies (199, 200). The study had a higher proportion of Stage IIIB patients than others published and, of the intended six courses of chemotherapy, only 43% of the gemcitabine–cisplatin group and 26% of the cisplatin–etoposide group received all six courses. The response rate was 41% for GC and 22% for CE. This study, like all modern studies, did attempt to measure quality of life. The authors used the EORTC QLC-LC13 questionnaire and showed no differences between baseline values between the arms or during treatment in functional parameters (physical role, cognitive, emotional, and social) or global quality of life. Both groups recorded a significant improvement in pain, insomnia, cough, hemoptysis, chest pain, and shoulder pain, but no improvement in dyspnea or fatigue. Despite GC producing higher responses, there was no survival advantage, despite a longer time to disease progression on this arm. Toxicity differences were only with nausea and vomiting for GC and alopecia with CE. It is disappointing that the response rate with chemotherapy does not seem to be a reliable surrogate marker of success and longer survival.

Another study looked at gemcitabine and cisplatin versus a reasonably high dose of cisplatin alone (201). This is one of three more recent studies that have confirmed that cisplatin combinations are better than cisplatin alone. A comparison of cisplatin with and without vinorelbine in 432 patients with advanced NSCLC found a better response (26 versus 12%) and median survival (35 versus 26 weeks) with the combination, although it caused more myelotoxicity (202). A combination of cisplatin with and without tirapazimine in 446 patients with advanced disease also found significant benefits with a combined treatment for response rate (28 versus 14%) and median survival (35 versus 28 weeks), but again with more adverse events (Table 4) (203). These data confirm earlier meta-analyses showing combination chemotherapy to be a little better than single-agent chemotherapy. There is also no evidence of a dose–response effect with cisplatin and similar median survivals and 1-year survivals were obtained by Sandler and coworkers using

TABLE 4. RANDOMIZED CONTROLLED TRIALS OF CHEMOTHERAPY REGIMENS AND THEIR EFFECTS IN ADVANCED NON–SMALL CELL LUNG CANCER

Study (Ref.)	Chemotherapy	Length of Cycle (d)	Courses	n	Stage III/IV	Mean Survival (mo)	Survival at 1 yr (%)	p Value
Cardenal and coworkers (198)	G, 1,250 mg/m^2, d 1–8 C, 100 mg/m^2, d 1	21	43% × 6	69	33/36	8.7	32	NS
	versus							
	C, 100 mg/m^2, d 1 E, 100 mg/m^2, d 1–3	21	26% × 6	66	34/32	7.2	26	
Sandler and coworkers (201)	G, 1,000 mg/m^2, d 1, 8, 15 C, 100 mg/m^2, d 1	28	6 mean DI G = 769 mg/m^2 C = 97 mg/m^2	260	84/174	9.1	39	0.004
	versus							
	C, 100 mg/m^2, d 1	28	6 mean DI C = 98 mg/m^2	262	88/184	7.6	28	
von Pawel and coworkers (203)	T, 390 mg/m^2 C, 75 mg/m^2	21	8 maximum	219	39/179	9.5	34	0.008
	versus							
	C, 75 mg/m^2	21		219	35/183	7	23	
Bonomi and coworkers (205)	P, 135 mg/m^2 C, 75 mg/m^2	21	Not stated	190	40/150	9.5	37	0.048
	versus							
	P, 250 mg/m^2 C, 75 mg/m^2	21	At least 2	191	35/156	10	40	
	versus							
	E, 100 mg/m^2, d 1–3 C, 75 mg/m^2	21		193	28/165	7.6	32	
Comella and coworkers (207)	C, 50 mg/m^2 G, 1,000 mg/m^2 VNR, 25 mg/m^2, d 1, 8	21	Up to 5	60	26/34	11.75	45	0.006
	versus							
	C, 100 mg/m^2 G, 1,000 mg/m^2, d 1, 8	28		60	26/34	10	46	
	versus							
	C, 120 mg/m^2 VNR, 30 mg/m^2/wk	28		60	24/36	9	34	
Sculier and coworkers (208)	M, 6 mg/m^2 I, 3 g/m^2 C, 50 mg/m^2	21	All got 3, then to best response or progression or toxicity	147	4/143	6.5	24	NS
	versus							
	M, 6 mg/m^2 I, 3 g/m^2 C, 60 mg/m^2 Carbo, 200 mg/m^2	21		150	4/146	7.5	23	

cisplatin at 100 mg/m^2 (201), as in the study by von Pawel and coworkers using cisplatin at 75 mg/m^2 (203).

However, the most recent study assessed cisplatin alone (100 mg/m^2), this time versus paclitaxel with cisplatin (Table 4) (204) in a similar population of mainly Stage IV disease patients, and found equivalent median survivals and 1-year survivals using the single agent, although once again the combination arm had a longer period before disease progression and similar quality of life data.

The role of paclitaxel and best dosage was explored in a large study by Bonomi and coworkers (205). Earlier Phase II studies using paclitaxel at 250 mg/m^2 over 24 hours every 3 weeks resulted in a 21% response rate, and a 40% survival at 1 year. They chose to test the effect on survival of paclitaxel combined with cisplatin compared with a standard regimen of etoposide and cisplatin at 75 mg/m^2. They chose CE as it had produced the highest 1-year survival rate (25%) in earlier Phase III studies (206). There was a higher proportion of Stage IV patients in the study (Table 4) and it showed no difference in effect for the two

taxol doses, but each taxol arm was significantly better than the CE arm. Quality of life was assessed with the FACT-L instrument immediately before chemotherapy and at 6, 12, and 24 weeks. Although there was no difference in scores between the three arms, all deteriorated over the 6 months of study. Only 11–20% of patients recorded improved quality of life during chemotherapy. Although this study was positive for paclitaxel–cisplatin, a large study of 1,207 patients has been published that compares cisplatin–paclitaxel, cisplatin–gemcitabine, cisplatin–docetaxel, and carboplatin–paclitaxel, obtaining response rates of 21, 21, 17, and 16%, respectively, and median survivals of 7.8, 8.1, 7.4, and 8.1 months, respectively, in patients with advanced disease, showing no particular advantage for any of these regimens (197) (Table 4). These responses were all PRs and many fewer than reported in Phase II studies. The median ages were 62–64 years in the 4 groups. Although the gemcitabine/cisplatin arm was associated with a significantly longer time to disease progression, it was also more likely to cause serious toxicity.

The study by Comella and coworkers (207) added vinorelbine

TABLE 4. CONTINUED

Study (Ref.)	Chemotherapy	Length of Cycle (d)	Courses	n	Stage III/IV	Mean Survival (mo)	Survival at 1 yr (%)	p Value
Gatzemeier and coworkers (204)	C, 100 mg/m²	21	All got 3, then up to 6	207	64/143	8.6	36	NS
	versus							
	P, 175 mg/m² C, 80 mg/m²	21		207	64/143	8.1	30	
Smith and coworkers (190)	M, 8 mg/m² V, 6 mg/m² C, 50 mg/m²	21	3	155	69/86	6	22	NS
	versus							
	M, 8 mg/m² V, 6 mg/m² C, 50 mg/m²	21	6	153	72/81	7	25	
Kelly and coworkers (210)	VNR, 25 mg/m²/wk C, 100 mg/m²	28	6–10	202	22/180	8	36	NS
	versus							
	P, 225 mg/m² Carbo, AUC 6	21		206	24/182	8	38	
Schiller and coworkers (197)	C, 75 mg/m² P, 135 mg/m² over 24 h	21	Assess every 2 courses	288	11/89	7.8	31	NS
	versus							
	C, 100 mg/m² G, 1,000 mg/m², d 1, 8, 21	28	Maximum not stated	288	14/86	8.1	36	
	versus							
	C, 75 mg/m² D, 75 mg/m²	21		289	14/86	7.4	31	
	versus							
	Carbo, AUC 6 P, 225 mg/m² over 3 h	21		290	14/86	8.1	34	

Definition of abbreviations: AUC = area under curve; C = cisplatin; Carbo = carboplatin; D = docetaxel; DI = dose intensity; E = etoposide; G = gemcitabine; I = ifosfamide; M = mitomycin; NS = not significant; P = paclitaxel; T = tirapazamine; V = vinblastine; VNR = vinorelbine.

to cisplatin and gemcitabine and compared this with cisplatin and gemcitabine alone and with cisplatin plus vinorelbine in a smaller study of 60 patients per arm with only 55% of subjects having Stage IV disease. A stratified Cox analysis predicted a significant reduction in HR for death with the cisplatin–gemcitabine–vinorelbine arm. Quality of life was measured as just a 10-item Lung Cancer Symptom Scale, but only toxicity data are detailed in the publication, with a trend to a high incidence for Grade 3 or 4 toxicity in the paclitaxel–vinorelbine arm.

The study by Sculier and coworkers (208) examines a standard European regimen, MIC, and the efficacy of a higher platin dose, adding carboplatin to cisplatin. There was no benefit, the study showing results comparable to those of other studies of MIC in patients with Stage IV disease (178).

The study by Smith and coworkers (190) looked at short-course chemotherapy consisting of MVC (another regimen commonly applied in the UK) administered to patients with Stage IIIB and IV disease, with slightly greater numbers presenting with Stage IV disease. They found no benefit for six courses versus three, with a deterioration in quality of life with longer treatment due mainly to an increase in chemotherapy-related side effects. Similarly, Socinski and coworkers, in a study of Stage IIB/IV NSCLC, showed no benefit of continuous paclitaxel and carboplatin until progression, compared with treatment limited to four cycles of the same agents (209).

The SWOG trial (210) followed an earlier study that confirmed the efficacy of vinorelbine and cisplatin in advanced disease (202) and compared vinorelbine and cisplatin with paclitaxel and carboplatin in predominantly patients with Stage IV disease. The median survival was 8 months in both arms and similar at 1 year (Table 4), but the vinorelbine arm was significantly more toxic.

Although almost all combinations of chemotherapy contain a platin, Georgoulias and coworkers (211) compared docetaxel with cisplatin (80 mg/m²) and with gemcitabine (1,100 mg/m², Days 1 and 8). The docetaxel dose was 100 mg/m², and 441 patients with Stage IIIB disease (36%) and Stage IV disease (64%) entered the study. There was no difference in outcome. Median survivals were similar, 10 months for docetaxel–cisplatin and 9.5 months for docetaxel–gemcitabine, with response rates of 32 and 30%, respectively.

What do all these studies show? Perhaps that the newer agents are a little more active and produce marginally better median and 1-year survivals. The standard regimens of the early 1990s, that is, MVC, MIC, and CE, produced median survivals for patients with mainly Stage IV disease of 6–8 months, with 25–30% of patients alive at 1 year; the newer agents, in combination mostly with platins, have extended median survival to 7–10 months with up to 40% of patients alive at 1 year. There seems no dose–response relationship to better survival with any of these drugs, and higher doses cause more and worse toxicity. There is no clear advantage of a platin combined with paclitaxel, gemcitabine, or vinorelbine. However, an oral form of vinorelbine will soon be available and is certain to be thoroughly evaluated. In general, the larger the study, the more the median survival remains at about 8 months with 30% of patients alive at 1 year.

Much of the quality of life data presented in these large studies is rudimentary and little effort has been made to determine what quality of life means to patients; we just score predominantly physical symptoms. Finally, cost matters. The newer agents are considerably more expensive than MIC and MVC regimens, but this is to some extent offset by day case administration. However, increasing the use of chemotherapy in advanced

TABLE 5. ACTIVE SINGLE AGENTS IN SMALL CELL LUNG CANCER

Established Agents	Newer Agents
Cyclophosphamide	Teniposide
Ifosfamide	Paclitaxel
Methotrexate	Docetaxel
Adriamycin (doxorubicin)	Vinorelbine
Vincristine	Germcitabine
Vindesine	Irinotecan
Etoposide	
Cisplatin	
Carboplatin	

NSCLC (which seems the current trend) will have a significant cost effect. Great care is needed to consider who should receive chemotherapy, clearly those with good performance status only, yet there remains the dilemma of giving four to six courses of chemotherapy to relatively fit cancer sufferers and turning them into patients having chemotherapy for a mean prolongation of life of just about 4 months.

SMALL CELL LUNG CANCER

In general, this cell type comprises 20% of all lung cancers. It is almost invariably disseminated or at least so locally advanced at the time of diagnosis as to be virtually always unresectable. It has the property of being extremely sensitive to cytotoxic chemotherapy. However, what appeared to be an exciting area of development and research in the mid-1970s, when chemotherapy was first applied to this tumor, has failed to make the progress that seemed probable 20 years ago. Thousands of studies looking at every variety of cytotoxic agent in varying dose schedules and combinations have shown that most regimens have similar response rates provided that at least two active drugs are given for at least four cycles. Advances have been made toward minimizing the toxicity of treatment and adding to the convenience of schedules, so that they have become predominantly outpatient based. Attempts to alternate different regimens, to overcome potential cross-resistance, or to try more intensive regimens at the start or the end of the program have had little impact.

Chemotherapy

Small cell lung cancer (SCLC) is sensitive to several chemotherapeutic agents, and most if given as single agents will elicit at least a partial response (50% or greater reduction in tumor size) in more than 30% of previously untreated patients. Several new agents have shown similar activity (Table 5). A plethora of studies in the 1970s showed combinations of agents to be superior to single agents both in terms of the response rates and the duration of the response and prolongation of survival (212, 213). Several combination regimens have shown acceptable and fairly similar activity, producing an objective response rate of 80 to 90%, with complete response (no tumor detectable on restaging tests) in up to 50% of patients, depending on the stage of presentation. Patients presenting with limited stage disease (disease confined to the hemithorax and including the ipsilateral supraclavicular fossa) do better than those with extensive stage disease. Median survival averages up to 20 months for limited disease and up to 7 to 10 months for extensive disease after treatment compared with 3 months and 6 weeks for untreated limited disease and extensive disease, respectively.

The optimal duration of combination chemotherapy is probably six to eight cycles (214). One study from our group randomized patients to receive four or eight courses of chemotherapy with a further randomization to receive, or not receive, salvage chemotherapy with different drugs at relapse. This showed a small survival disadvantage for those receiving only four cycles and no salvage treatment, but no advantage to additional therapy after eight cycles. Those receiving only four courses with a good response to treatment had a shorter disease-free interval (214). The UK Medical Research Council study (215) showed no difference in survival between 6 and 12 courses, although relapse occurred earlier with shorter treatment, but there was greater toxicity and poorer quality of life measures with the prolonged treatment In our study, quality of life improved temporarily, particularly when chemotherapy was stopped after four courses (214). Most centers now treat SCLC with six courses of combination chemotherapy, as fewer treatments seem to reduce the disease-free interval after chemotherapy, thus less than six cycles disadvantages those patients who have the best responses.

The topic of maintenance therapy has been carefully examined and several RCTs confirm that four to six courses of treatment is as effective as prolonged chemotherapy (216, 217).

Long-term results after chemotherapy remain disappointing. In a nation-wide UK study of all patients entered into clinical trials between 1978 and 1986, only 5.6% of patients were alive at 2 years (limited disease, 8.5% and extensive disease, 2.2%) (218). Of 1,714 Danish patients treated by chemotherapy between 1973 and 1987, 3.5 and 1.8% were alive and disease free at 5 and 10 years, respectively (219). Age at diagnosis had no influence on likelihood of survival, and only 184 received mediastinal radiotherapy. Deaths from SCLC continue until 7 years, at which time 3% of patients are alive and deaths from SCLC cease, although deaths from other smoking-related causes continue, most notably NSCLC (218).

Criteria have been identified for patients who have a realistic chance of living 2 years and those who are likely to die quickly (220–223). Apart from disease extent, performance status, serum alkaline phosphatase, plasma albumin, and sodium concentrations carry independent prognostic information. Serum lactate dehydrogenase can be substituted for alkaline phosphatase. Taken together, these simple serum analyses and performance status give more prognostic information than disease extent defined by more detailed and expensive imaging tests. The value of prognostic factors is that they identify patients with a chance of cure, but also patients with limited disease at risk of early death and patients with extensive disease with a chance of living 18 months with chemotherapy; and they help to facilitate comparisons between trials.

Although the toxicity from chemotherapy is well understood and to a considerable extent predictable, the side effects can be a major problem and a dose-limiting factor, particularly in an increasingly elderly population of patients. Toxic deaths remain generally few but they increase as attempts are made to intensify chemotherapy to improve response rates and median survival. Some patients have a particularly high risk of death after the first chemotherapy cycle (224). These are patients with hepatomegaly, low plasma albumin, high alkaline phosphatase, and poor performance status. Mortality was due to neutropenic sepsis and occurred in 10% of 616 patients in one study (224). It was subsequently eliminated by recognizing these risk factors and administering antibiotics routinely around the neutrophil nadir period. The mortality appeared to be related to etoposide-containing chemotherapy and occurred 7 to 15 days after administration. Similar findings were also noted by the MRC when using a regimen containing etoposide (215).

Overall, no single combination regimen has been found to be ideal or clearly superior. During the 1970s and 1980s, cyclophosphamide-based regimens were used commonly, usually with Adriamycin (doxorubicin) and vincristine (CAV) (225). More

recently, induction regimens have moved to include etoposide either as a substitution for one of the components of CAV, or more usually with cisplatin. A common therapy is CAV alternating with platinum and etoposide (PE) or PE on its own. Direct comparisons between CAV alone and PE have failed to show a useful difference (226, 227). However, a meta-analysis of randomized controlled trials comparing all regimens containing or not containing cisplatin (228) found that although there was no difference in toxicity, patients treated with a cisplatin-containing regimen had a significant reduction in the risk of death at 6 and 12 months. This translated into a survival benefit of 2.6 and 4.4% at 6 and 12 months, respectively.

Carboplatin when combined with etoposide appears as effective as cisplatin and etoposide, with less toxicity (apart from increased myelosuppression) (229). The Hellenic Oncology Group also conducted a Phase III RCT of carboplatin–etoposide and cisplatin–etoposide in both limited and extensive stage patients. The median survivals of about 12 months were similar in both arms (230).

The choice of regimen outside a clinical trial depends on the patient's potential tolerance of the chemotherapy. For example, cisplatin may be contraindicated because of inadequate renal function, or significant pre-existing peripheral neuropathy. Heart disease may make the hydration necessary for platinum regimens difficult. Here carboplatin would be an alternative. Similarly, Adriamycin is contraindicated in the presence of heart disease and should be avoided after radiotherapy to the chest because it enhances postradiation pneumonitis. *Vinca* alkaloids should also be avoided if there is a pre-existing neuropathy.

Dose intensification. In tumor models one of the simplest ways to overcome drug resistance is dose intensification. In the 1970s Cohen and coworkers conducted a series of trials with increasing doses of cyclophosphamide and lomustine with standard doses of methotrexate (231). They observed a higher response rate and prolonged survival in the high-dose arm. Also, longer term survival was seen only in the high-dose group. By today's standards the doses used would appear modest, but they introduced the concept of high-dose chemotherapy for this disease.

Our group was among the first to attempt high-dose induction chemotherapy with autologous bone marrow support. Cyclophosphamide (200 mg/kg) was given to good performance patients with limited disease, but although this and three other uncontrolled pilot studies achieved responses rates of 90%, the survival was no better than among similar patients treated on study by conventional cyclical chemotherapy (232). Our results were similar to those of others (233, 234) and on the basis of these data, this procedure does not appear to be justified.

Other groups have compared conventional dose treatment with a more intensive regimen (235–238). Overall, patients with extensive disease fared badly, with a greater incidence of Grade IV toxicities, in particular neutropenia, and the approach has become confined to those with limited disease. However, the impact on survival was modest and similar to the conventional arm in each of the studies except that of Arriagada and coworkers (238). They performed a randomized study of patients with limited disease, using conventional dose cisplatin, cyclophosphamide, etoposide, and doxorubicin alternating with thoracic radiotherapy, versus the same regimen except that the doses of cyclophosphamide and cisplatin were 20% higher for just the first treatment cycle. The 2-year survival was significantly higher in the dose-intensive group (43 versus 26%) (238). Another study giving vincristine, ifosfamide, carboplatin, and etoposide every 3 or 4 weeks to patients with limited disease showed no survival advantage for either group. Both groups were also randomized to receive granulocyte-macrophage colony-stimulating factor

(GM-CSF) or no support. The addition of GM-CSF did not reduce the incidence of myelosuppression or have any effect on survival (239). However, the improved rate of recovery with these factors does allow for a potential increase in dose intensity, that is, doses in milligrams per meter squared per week.

Another study of extensive stage patients gave higher doses of cyclophosphamide, epirubicin, etoposide, and cisplatin with GM-CSF, versus the same drugs in lower doses without GM-CSF, and failed to show a survival advantage (240). Thatcher and coworkers (241) randomized 403 patients to receive either six cycles of doxorubicin, cyclophosphamide, and etoposide every 3 weeks, or the same regimen plus G-CSF every 2 weeks. The latter group achieved a dose intensification of 34%. The complete response rate was higher in the G-CSF group (40 versus 28%) and the survival was better; 47 versus 39% at 12 months and 13 and 8% at 2 years. Quality of life measures were similar in the two groups, but the G-CSF patients had more thrombocytopenia and more blood transfusions.

Weekly chemotherapy. The concept of increasing intensity by more frequent administration of chemotherapy has resulted in trials comparing conventional 3-weekly with weekly regimens. Our study included 438 patients with limited disease and good prognosis, extensive disease who were randomized to receive 12 courses of weekly ifosfamide and doxorubicin alternating with cisplatin and etoposide versus 6 cycles of CAV alternating with etoposide and cisplatin every 3 weeks (241A). There was no survival benefit for the intensively treated group. Similar results were described by other groups comparing weekly with conventional therapy (242–244). However, one of the difficulties with weekly chemotherapy was in achieving administration of the intended dose, which in our group's study was only 71% of intended in the weekly group.

Late intensification chemotherapy. There are theoretical advantages for late intensification, as initially patients are ill and symptomatic as a consequence of the extent of their disease. Patients achieving a complete response with induction chemotherapy might be good candidates for high-dose consolidation treatment. However, the results of this approach contain few comparative data as the cases treated tend to be selected from the responders and the attrition rate from toxicity is high, with only a small number of patients achieving the intended treatment (245, 246). No useful survival advantage has been reported from late intensification studies.

Single-agent chemotherapy. Preliminary assessment of oral etoposide given as a single agent gave response rates and survival times similar to combination regimens. These data were also obtained in elderly groups and in those considered too ill for standard combination chemotherapy (247, 248). However, three randomized trials of oral etoposide versus conventional 3-weekly intravenous chemotherapy have reported worse survival with etoposide. In the first study patients with extensive disease were randomized to etoposide (130 mg/m^2 per day) and cisplatin (25 mg/m^2 per day) on Days 1–3, versus oral etoposide (50 mg/m^2 per day) for 21 days plus cisplatin (33 mg/m^2 on Days 1–3). There were no differences in response rates or median survival, but hematologic toxicity was greater among patients receiving oral etoposide (249).

The UK MRC compared single-agent oral etoposide at 50 mg twice daily for 10 days every 3 weeks with conventional 3-weekly intravenous combination chemotherapy, in 339 patients with poor performance status (250). The conventional treatment group had a better response rate and median survival, again showing inferior results for the oral etoposide group. Our study of a 5-day oral etoposide regimen compared with conventional three-drug treatment was stopped after 155 patients were entered because an interim analysis advised closure of the study

as the 1-year survival, progression-free intervals and quality of life data were inferior with etoposide (251). These data confirmed the value of randomized studies, as oral etoposide was being commonly used to palliate elderly or ill patients and threatened to become the standard treatment off study for patients with extensive disease. There is therefore no justification in using oral etoposide as a single agent in patients fit to receive chemotherapy.

Treatment of Limited Disease

Limited disease SCLC is treated by combination chemotherapy and chest irradiation. There were many trials performed in the 1980s of chemotherapy alone versus chemotherapy with the addition of radiotherapy. The trials were of various designs and differed in patient selection as well as in size of the radiotherapy field, dose administered, and the timing of the treatment in relation to the chemotherapy. Some studies included patients with extensive disease, others included those with limited disease only but with bulky intrathoracic disease before chemotherapy, and some had pleural effusions or ipsilateral supraclavicular lymphadenopathy. There was also debate as to whether the chosen radiotherapy field should be that covering the initial disease extent before chemotherapy, or that after the response to chemotherapy. Most studies chose the latter, and treated the area of residual disease and included the mediastinum, and radiotherapy was usually given after three to six courses of chemotherapy, but in some was concurrent with the first course of chemotherapy.

Two meta-analyses in 1992 ended a considerable debate as to the potential value of chest irradiation (252, 253). Warde and Payne went through all the published papers and Pignon and coworkers reviewed all the raw data. The outcomes were similar and both proved a small but significant advantage in survival for receiving radiotherapy, with an advantage of 5.4% at 3 years after commencing treatment. In the analysis by Pignon and coworkers, 14.3% of 1,111 patients who received the combined treatment survived 3 years compared with 8.9% of 992 patients who received chemotherapy alone (252).

More recently, the 3-year survival rates have climbed to between 20 and 30% for chemoirradiation. There are several factors that may have contributed to this. CT scanning has been increasingly incorporated into optimizing the radiation field. Since the early 1980s cisplatin and etoposide have been increasingly replacing the older cyclophosphamide and Adriamycin regimens with much less irradiation toxicity, as platins and etoposide have shown a lesser tendency to increase toxicity in association with radiation. The advantage that radiotherapy confers is better local disease control; for example, in one large review, the local relapse rates were 33% after radiotherapy alone, 28% after chemotherapy followed by radiotherapy, and 82% after chemotherapy alone (254).

Integral to the improvements in the survival of patients undergoing multimodal therapy are the possible benefits of research into the sequencing of radiotherapy with chemotherapy, the timing of treatment, and the fractionation regimens.

The sequence. In studies in which irradiation followed the completion of chemotherapy there was no survival benefit, even if the irradiated field was reduced to that of the postchemotherapy tumor volume. The 2-year survival was less than 20% for either arm (255–257).

Alternating therapies with 1 or 2 weeks in between allows recovery and minimizes toxicity. This approach was tested in a randomized study in which radiotherapy after five courses of chemotherapy was compared with the irradiation being given concurrently in four short courses between each of the second to fifth courses of chemotherapy. The 3-year survival rates of 15

and 12%, respectively, were similar, and the alternating sequence less toxic (257). Another study of similar design was also negative (258).

Concurrent administration of chemotherapy and radiotherapy has been evaluated to explore synergism between therapies, although choice of drugs is an important factor because of potential additional toxicity. Cisplatin and etoposide seem to be the choice among agents because of the absence of cardiac, esophageal, or pulmonary toxicity. Studies have shown that this approach has reported improved survival rates of 40% at 2 years (259).

Timing. There are five trials that have addressed the question of timing of radiotherapy (260–264). The three-arm Cancer and Leukemia Group B (CALGB) study included 399 patients with limited disease randomized to chemotherapy alone, or 50 Gy of thoracic radiation and whole brain irradiation with the first course of chemotherapy, or to thoracic and brain irradiation at Week 9 with the fourth course (260). There was no difference between the two multimodality arms. In the study by Work and coworkers 199 patients were given chest irradiation at the start of chemotherapy or at Week 18. Radiotherapy was with 40–45 Gy and the two arms had similar survivals (262). A study by the National Cancer Institute of Canada (261) treated 309 patients with 6 cycles of chemotherapy comprising alternating courses of CAV and PE. Patients received 40 Gy of radiotherapy to the primary site concurrent with the second or sixth course of chemotherapy. Dose intensities in the two arms were similar, as were the complete response rates. However, there was a significant survival advantage for the early radiotherapy arm, with a median survival of 21.2 months for the early arm and 16 months for the late arm. The 5-year survival was 22 and 13%, respectively.

A Yugoslavian study assessed both the timing and the fractionation of radiotherapy. All patients received accelerated hyperfractionated therapy twice daily to 54 Gy, with concurrent daily carboplatin and etoposide, and also four cycles of these two drugs. Early irradiation was between Weeks 1 and 4, and the other group received radiation and concurrent chemotherapy between Weeks 6 and 9, that is, 6 weeks later. The median survival was 34 months for the early arm and 26 months for the late arm, with 5-year survival of 30 and 15%, respectively (263). Finally, a Japanese study also randomized patients to initial concurrent versus sequential irradiation. Again, initial radiation was significantly superior, with median survivals of 31 and 21 months and projected 5-year survival of 30 and 15%, respectively (264).

This remains an interesting and potentially important approach. The negative trials have been criticized as including poorer prognosis patients and patient selection plays a critical role in the outcome of studies such as these. Our group has just completed repeating precisely the National Cancer Institute of Canada study, to accruing 320 patients in an attempt to confirm the earlier study and to evaluate a combined data set of 700 patients.

Dose and fractionation. The dose response for SCLC is poorly defined. Although it is a sensitive tumor, local recurrence is common. It seems that the higher the radiation dose the better the local control: for example, local control rates at 2.5 years in one review of 16% after 30 Gy, 51% after 40 Gy, and 63% after 50 Gy (265).

The effect of change in fractionation was evaluated by Turrisi and coworkers (266) in a randomized study in which patients with limited disease were treated initially with PE and 45 Gy in 5 weeks with a daily fraction of 1.8 or 45 Gy in 3 weeks with two fractions of 1.5 Gy each day. Toxicity was greater in the arm receiving two fractions a day, but the survival at 3 and 5

years was 27 and 20%, respectively, for the daily treatment and 31 and 28% for the twice-daily regimen. Local control was also better maintained by the two-treatment schedule. The study by Jeremic and coworkers reported above, which examined the timing of radiation, included a hyperfractionated regimen in both arms but showed a promising overall response to hyperfractionated treatment. Local failure after hyperfractionation remains high and studies are examining the potential of doses in the region of 60 Gy (263).

Radiation improves the effects of chemotherapy in limited disease but the major influence on the results obtained will be patient selection, and more studies will be required to obtain a critical mass of data. Patients in pioneering novel studies tend to be fitter and younger than the average sufferer of the disease.

Extensive Disease

The outlook for patients with extensive disease is far worse than that for patients with limited disease. In a review of 20 Phase III trials of chemotherapy in extensive disease there was an improvement in survival data when comparing trials between 1972–1981 and 1982–1990. Median survival rose from 7.0 to 8.9 months (267). Treatment with cisplatin and the year the study started were significantly correlated with better survival. Another review (268) looked at regimens of different intensity and concluded that patients had better survival chances with aggressive regimens than with a minimal approach. However, there is a balance to be struck between toxicity and survival, as patients with extensive disease are unlikely to live for many months even with chemotherapy and "aggression" must be reviewed in this light, that is, there must be a toxicity-to-benefit ratio.

A Phase II study of irinotecan plus cisplatin yielded a CR of 29% and an overall response rate of 86% with a median survival of 13.2 months in patients with extensive disease SCLC (269). This has led to an RCT of irinotecan and cisplatin versus etoposide and cisplatin in patients with extensive disease SCLC. The study was halted early because of a significant survival advantage for the patients randomized to irinotecan plus cisplatin (median survival of 12.8 versus 9.4 months) (270). The 2-year survival was 19.5 and 5.2%, respectively. The etoposide–cisplatin arm was more myelotoxic (65 versus 25% of Grade 4 neutropenia), but the irinotecan–cisplatin arm had a higher incidence of severe or life-threatening diarrhea (5.3 versus 0% of Grade 4 toxicity). Approximately, 70% of patients in both groups received the intended four courses of treatment, and irinotecan plus cisplatin appears to be a more effective treatment for patients with extensive disease.

Although cisplatin and etoposide remain the commonest choice for combination chemotherapy for patients with extensive disease, the issue of adding a third drug has been examined. Adding ifosfamide to CE versus CE alone in 171 patients with extensive disease caused an increase in 2-year survival from 5 to 13%, but with increased toxicity (271). Another study of cisplatin, etoposide, and paclitaxel compared with CE was stopped early because of a high toxic death rate in the 3-day arm, with no overall survival benefit (272).

Elderly Patients

Elderly patients are generally considered those aged 70 years or greater. Until the early 1990s trials had an upper age limit of 70 years, and little was known about how this important group of patients reacted to treatment. Either chemotherapy suitable for younger patients was given or, more commonly, treatment was of minimal intensity despite accumulating knowledge that minimizing the intensity of chemotherapy resulted in fewer responses and also responses of shorter duration. Nevertheless, a more pragmatic approach needs to be taken as the elderly have a greater incidence of comorbidities including heart disease, cerebrovascular disease, renal problems, ambulatory difficulties, and diabetes and are often the surviving partner and may live alone, often with minimal support, making intensive chemotherapy or radiotherapy inappropriate. There are as yet no guidelines as to the best treatment for the elderly. They are disadvantaged, as studies assessing the diagnosis rates in new patients with lung cancer show that the diagnosis is made less often in those over 70 years of age, they are not always seen by a respiratory specialist, and a smaller percentage are referred for surgery, radiotherapy, and chemotherapy (41). Furthermore, the elderly are appropriately staged in fewer numbers than expected and are underrepresented in units where treatment is given (*see* above). Dajczman, in a review of treatment given in Quebec, found that suboptimal treatment was given to 26% of those over 70 years of age, compared with 9% of patients aged 60–69 years of age and 5% of those under 60 years of age (273). Chemotherapy plus radiotherapy was given to 43, 65, and 69% of patients with limited disease in the three age groups, respectively. Response and survival data reflected the treatment decisions, with CR or PR seen in 25, 49, and 41% of the three age groups and median survivals of 6, 9, and 8.5 months, respectively.

The palliative approach of single-agent chemotherapy as a more gentle form of treatment was given to patients with poor prognosis SCLC and trials included elderly patients. As discussed above, comparisons of single-agent therapy, in particular oral etoposide, when compared with conventional multiagent chemotherapy produced inferior survival and quality of life data, causing the studies to be stopped early (250, 251).

The optimal management of the elderly with SCLC is an important issue as 40% of those who present with the disease are over 70 years old. Studies that investigated this area suggest that a reasonably high initial dose of chemotherapy is important and that the elderly tolerate radiotherapy well (274–276). Indeed, elderly patients with good performance status and normal organ function do as well with optimal chemotherapy doses as their younger counterparts (277). Greater support will be required, and there may be more enforced treatment delays, but without reducing outcome.

Prophylactic Cranial Irradiation

Patients who achieve a CR have a cumulative risk of 50% of developing a brain metastasis, often as the first site of relapse. Survival after a brain relapse is short with high morbidity and much of the remaining life in care (278). The rate of cerebral relapse is halved if prophylactic cranial irradiation (PCI) is given after a CR to initial treatment (279, 280), but it has not been certain whether this also prolongs survival. A meta-analysis answered this question (281) by looking at 987 patients from seven RCTs. The cumulative incidence of brain metastases 3 years after randomization was half in the patients receiving PCI (33 versus 59%). The risk of death was reduced by 16% in the PCI group and the survival benefit persisted at 6 years. It is therefore recommended that patients achieving a CR undergo PCI, although there is still debate over the optimal dose (282), and this is the subject of a current European study randomizing to a high dose of 40 Gy or a moderate dose of 25 Gy.

One of the main concerns was of late neurotoxicity in the early trials of PCI, with deterioration of quality of life. More recent trials have assessed cognitive ability before and after PCI and failed to show deterioration from pretreatment baseline up to 2 years after treatment (279, 283), including careful investigation up to 2 years after treatment with CT and MRI and neurophysiologic testing with matched control subjects (284).

DETECTION OF EARLY LUNG CANCER AND PHOTODYNAMIC THERAPY

If progress is to be made in the early detection and treatment of lung cancer then we need to detect lesions before they become invasive. The World Health Organization has published the third edition of *International Histological Classification of Tumors* (285) (reviewed in [286]) and lists three main forms of preinvasive lesion in the lung: (*1*) squamous dysplasia/carcinoma *in situ* (SD/CIS), (*2*) atypical adenomatous hyperplasia (AAH), and (*3*) diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). SD/CIS is graded into four stages (mild, moderate, severe and CIS). Little is known about the progression of these lesions, but it is generally thought that squamous cell carcinomas have their origin in SD/CIS, and there is reasonable morphologic evidence that AAH may progresses through low to high grade and then to bronchoalveolar cell carcinoma (a noninvasive lesion) and finally peripheral adenocarcinoma (286, 287). DIPNECH is rare and associated with the development of multiple carcinoid tumors. A knowledge of these preinvasive lesions and how they might evolve is essential in interpreting the results of studies that aim to detect and treat them early. Attention has focused on detection of early central squamous cell lesions (SD/CIS); it is less clear how peripheral lesions such as AAH might be detected.

The development of fluorescence bronchoscopy is considered to be one of the most important new initiatives in the detection of early squamous cell lung cancer. Although traditional white light bronchoscopy has a yield of greater than 90% for picking up macroscopic lesions (288), it is less good at picking up SD/CIS. It has been recognized for some time that dysplastic and malignant cells exposed to light of a specific frequency will emit light of a wavelength different from that of normal tissue. Fluorescence bronchoscopy takes advantage of this difference and uses a blue light for illumination. Under this illumination premalignant and malignant tissues give off slightly weaker red fluorescence but much weaker green fluorescence than normal tissues, which can be recognized by an experienced operator (289). SD/CIS and early invasive lesions detected by fluorescence bronchoscopy are thought to be the earliest manifestation of lung cancer and it is hoped that their detection and treatment will improve prognosis in a subsection of high-risk patients. False-positive abnormal fluorescence can occur in patients with suction trauma, bronchial asthma, severe mucous gland hyperplasia, or acute purulent bronchitis. Several systems are available for fluorescence bronchoscopy, of which the best known are the light-induced fluorescence endoscopy (LIFE) device (Xillix Technologies, Vancouver, BC, Canada [290]) the D-Light/AF system (Karl Storz, Tuttlingen, Germany [291]), and the SAFE-1000 (Pentax, Tokyo, Japan [292]).

Most of the large multicenter clinical trials comparing conventional white light bronchoscopy (WLB) followed by fluorescence examination have used the LIFE device, currently the only one approved by the U.S. Food and Drug Administration. In a study by Lam and coworkers of 173 subjects with known or suspected lung cancer, all patients underwent WLB followed by LIFE and the results of biopsies were compared. The relative sensitivity of WLB plus LIFE versus WLB alone was 6.3 for intraepithelial neoplastic (moderate/severe dysplasia and carcinoma *in situ*) lesions and 2.71 when invasive carcinomas were also included. However, only 95 of 285 biopsies taken from areas abnormal by LIFE contained abnormal histology, giving a high false-positive rate of 66% (293). The significance of suspicious findings with LIFE and negative histology is unknown, but two cases have been shown to progress to dysplasia and carcinoma, respectively (294). This suggests that abnormalities detected with LIFE might reflect molecular genetic abnormalities that are beyond the threshold of the microscopic abilities of the pathologist. One criticism of the study by Lam and coworkers is that LIFE was always preceded by WLB, which might have biased the results.

More recently, Hirsch and coworkers performed another randomized study of WLB versus LIFE to detect early lung lesions in 55 patients at high risk of lung cancer and found that the results were similar regardless of the order of the procedures or the order of the bronchoscopists (295). WLB and LIFE were performed on all patients and 391 biopsy specimens were taken. Moderate or severe dysplasia was seen in biopsies from 32 patients and LIFE was significantly more sensitive than WLB for detecting this (68.8 versus 21.9%, respectively). However, LIFE alone would have missed dysplasia in 10 of the 32 patients. Other studies have found no improvement in detecting preinvasive lesions using LIFE in conjunction with WLB despite screening a similar at-risk population (296, 297). Surprisingly, one of the studies found no moderate/severe dysplasia of CIS in any of the study patients (296). This variation in the reported detection rates of WLB and LIFE is probably related to differences in the patient population, the number of patients in the study, the skill of the bronchoscopists, and differences in pathology interpretation of dysplasia and CIS. It is hoped that the World Health Organization classification of preinvasive lung cancer (285) together with the development of objective quantitative image cytometry will further improve diagnostic accuracy and minimize interobserver variation. Although the cumulative evidence looks favorable (298), it is too early for fluorescence bronchoscopy to be considered outside its role as a research tool in the early detection of lung cancer until these differences have been resolved.

A new problem has been posed by these initiatives. What is the appropriate way to manage these intraepithelial lesions when they have been identified? It is widely assumed that metaplasia, dysplasia, and CIS are premalignant although histologic documentation of progression to invasive disease has proved difficult. LIFE technology has made it much easier to follow up such lesions and two large studies have published their findings. Venmans and coworkers followed up three patients with severe dysplasia and six patients with CIS. Of these, five patients (including four who had received endobronchial therapy) progressed to invasive carcinoma. The four patients who did not progress all had CIS; two resolved spontaneously and two had received endobronchial therapy (294). Bota and coworkers monitored 104 high-risk patients over a 2-year period with surveillance LIFE and all high-grade (severe dysplasia or CIS) lesions were treated. They monitored 59 high-grade lesions over 2 years and treated 35 lesions that showed persistent severe dysplasia or CIS. At the end of the 2-year period, 10 of 27 severe dysplastic lesions (37%) had persisted or progressed and 28 of 32 CIS lesions (87.5%) persisted. In addition, 11 of 27 severe dysplastic lesions (41%) and 3 of 33 CIS lesions (9%) were normal. The only lesion that became invasive over this time was an untreated metaplastic lesion in a patient with another CIS lesion at baseline (299). Unfortunately, neither of these studies can answer the question of what happens if high-grade lesions are left untreated to give a better understanding of the natural history of this disease.

Many of the patients who take part in screening studies for the early detection of lung cancer are chosen because of their high risk. In particular, many of them are current or ex-smokers who have undergone successful resection of a previous lung cancer. These patients have a 10% risk of developing a second lung tumor, and if they do it may be impractical to surgically remove more lung tissue. One nonsurgical method of treating early lung cancers is by endobronchial photodynamic therapy

(PDT) under local anesthesia and sedation. PDT is approved by the U.S. Food and Drug Administration for the endobronchial treatment of microinvasive NSCLC and for palliation in patients with obstructing tumors. A mixture of different porphyrin-based oligomers (such as Photofrin [porfimer sodium]) is injected intravenously, with care not to extravasate. The drug is cleared in 72 hours, but is retained for up to 30 days in tumors, skin, liver, and spleen. After 48 hours light with a wavelength of 630 nm is shone from a laser onto the tumor and the resulting phototoxic reaction destroys tumor to a depth of 5 to 10 mm. The light is delivered though a cylindrical diffuser fiber that is passed through the working channel of the flexible bronchoscope and the tip is then embedded into the lesion. The bronchoscopy should be repeated at 48 hours to clear debris and secretions and prevent compromise of the airway (a particular problem when treating tracheal lesions, and those requiring high energy levels). Another complication of PDT is skin photosensitivity. Patients are kept in special hospital rooms and are given advice before discharge such as to avoid even normal daylight for 4–6 weeks after the injection. Care should be taken when using pulse oximeters, which have caused severe finger-tip burns for monitoring patients during the procedure. PDT has been used to treat early lung cancers (less than 10 mm in diameter) with a cure rate of more than 75% (300–302). There is some early evidence that EBUS can be used to select for tumors in the large airways that are sufficiently localized (i.e., have not extended beyond the airway cartilage) to be treated by PDT with curative intent, as an alternative to surgery (303). In addition, McCaughan and coworkers treated 16 patients with Stage I NSCLC who were not candidates for surgery. The patients had a 93% 5-year survival (304). PDT has also been assessed for use as a palliative treatment and has been shown to perform as well as other modalities, in particular the Nd:YAG laser, in relieving endobronchial obstruction by NSCLC (304, 305). However, care must be taken as the time lag between treatment and tissue necrosis means that PDT is not suitable for emergency relief of obstruction, and in addition, obstruction may worsen because of the intense inflammatory response at 24–72 hours posttreatment, so that bronchoscopy and resuscitation equipment must be available.

THE FUTURE

The disappointing prognosis for patients with lung cancer has prompted nihilism on the one hand and determination to improve outcomes on the other. This has led to a search for new agents to complement the antitumor effects of chemotherapeutic drugs. Several observations of lung tumor biology have influenced the selection of candidate drugs, many of which have been designed to affect specific cellular pathways implicated in oncogenesis. Angiogenesis is thought to play an important role in tumor growth and metastasis. Successful blood vessel formation lies in a balance between proangiogenic factors, such as the growth factors vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), and epidermal growth factor (EGF) acting through their receptor tyrosine kinases; the degradation and remodeling of the extra cellular matrix by matrix metalloproteinases (MMPs) and their inhibitors, the tissue inhibitors of matrix metalloproteinases (TIMPs); and the naturally circulating antiangiogenic molecules angiostatin (306) and endostatin (307). Some observations in lung cancer itself have reinforced the idea that inhibiting angiogenesis might prove fruitful. For example, in a study of 143 patients with fully resected primary NSCLCs, the median survival of patients with angiostatin-negative/VEGF-positive tumors was significantly less than those with angiostatin-positive/VEGF-negative tumors, 52 versus 184 weeks, respectively. Intra-

tumoral microvessel density (IMD) has also been variably related to a poorer prognosis (308). Levels of cellular expression of VEGF (309–314) and its receptor (VEGFR), the EGF receptors (EGFR/HER-1/c-Erb-B1 [315–318] and HER-2/c-Erb-B2 [315–318]), and MMP-9 (317) have all been found to be increased in certain lung cancers, although how this relates to prognosis is still contentious (310–316, 319, 320).

At present many candidate molecules have been developed to inhibit angiogenic pathways in the hope of making an impact in cancer treatment, and this review considers those molecules that have reached Phase III trials.

The growth factors and their receptors are judged to have enormous potential as novel therapeutic targets. A Phase II trial of a recombinant humanized anti-VEGF antibody (rhuMAb-VEGF, Bevacizumab; Genentech, San Francisco, CA) in combination with paclitaxel and carboplatin in NSCLC was sufficiently encouraging that a large Phase III trial involving metastatic NSCLC is underway. Even more hope has been invested in the EGFR-blocking agents. The most extensively studied of these agents are (*1*) monoclonal antibodies against the extracellular domain of the receptor, including IMC-C225 (Erbitux; ImClone Systems, Somerville, NJ) directed against the EGFR and trastuzumab (Herceptin; Genentech) directed against HER-2/c-Erb-B2, and (*2*) inhibitors of the tyrosine kinase region of the receptors such as ZD 1839 (Iressa; AstraZeneca, Wilmington, DE) and OSI-774 (Tarceva; OSI Pharmaceuticals, Melville, NY). So far, only ZD 1839 and OSI-774 have progressed to Phase III studies in NSCLC. There are currently two multicenter Phase III trials of chemotherapy (carboplatin plus paclitaxel in one study, and cisplatin plus gemcitabine in the other) alone or in combination with ZD 1839 in newly diagnosed patients with advanced Stage III/IV NSCLC. Both trials completed enrolment of chemotherapy-naive patients in late 2001. Two similar Phase III studies are in early stages, and plan to compare chemotherapy (carboplatin plus paclitaxel in one study, and cisplatin plus gemcitabine in the other) alone or with OSI-774, again in chemotherapy-naive patients with advanced stage NSCLC. The primary end point for all four trials is survival.

To date, several potent synthetic inhibitors of MMPs (MMPIs) have been produced and tested in patients. Many of these made it to Phase III trials in advanced lung cancer but, disappointingly, most of these trials were halted following a poorer outcome in the treated group. It is not clear why the results were so poor, but it has been suggested that MMP inhibition is needed at the time of angiogenesis and not once the tumor microvasculature has been established. So that although a Phase III trial of one such agent, prinomastat (AG3340; Pfizer, New York, NY) in advanced (Stage IV) NSCLC was halted in August 2001, patients with earlier (Stage IIIB) disease are currently being recruited into a Phase II trial comparing standard chemotherapy with and without the MMPI. A Phase III trial of another MMPI, BMS-275291 (Bristol-Meyers Squibb, Princeton, NJ), in combination with paclitaxel and carboplatin, is currently open for patients with advanced NSCLC. Neovastat (AE-941; Aeterna, Quebec, PQ, Canada), a naturally occurring MMPI extracted from shark cartilage extract, significantly improved survival in patients with inoperable Stage III and IV NSCLC and recruitment has begun for a Phase III trial in inoperable Stage III NSCLC in combination with platinum-based chemotherapy (cisplatin and vinorelbine or carboplatin and paclitaxel) and radiotherapy. Another inhibitor of angiogenesis is carboxyamido-triazole (CAI); how it works is not entirely clear, although it is known to inhibit calcium-mediated signal transduction. A randomized Phase III study of oral CAI in patients with advanced NSCLC, who have received chemotherapy, is recruiting patients and aims to assess the safety of CAI and to collect data

on quality of life and time to progression. Thalidomide has been shown in preclinical models to be antiangiogenic, and although the exact mechanism is not understood it is thought to be involve effects on tumor necrosis factor-α and VEGF, among others (321, 322). A randomized trial of paclitaxel–carboplatin and radiation with or without thalidomide is open for patients with Stage IIIB NSCLC in the United States.

Another potential area of interest is that of apoptosis or programmed cell death and both apoptosis-protective molecules such as Bcl-2, and apoptosis-stimulating molecules such as Bax, are being pursued as targets for inhibition or activation, respectively. Genasense (formerly known as G-3139; Genta, Berkeley Heights, NJ), is an antisense oligonucleotide specific for Bcl-2; it is administered as an intravenous infusion and is in Phase III trials for malignant melanoma and earlier phase studies in NSCLC.

Another target is protein kinase C (PKC), and some encouraging results have been seen with Isis 3521 (Isis Pharmaceuticals, Carlsbad, CA), an antisense PKC inhibitor that binds to PKC-α RNA and prevents transcription. In Phase II studies, patients with Stage IIIB or IV NSCLC were treated with carboplatin–paclitaxel alone or with Isis 3521. Those that received Isis 3521 had a median survival of 19 months compared with 8 months for those not receiving the drug. A Phase III study of similar design is underway.

Other strategies have also been developed, such as vaccines directed against tumor-specific gangliosides; one such anti-idiotypic monoclonal antibody against the GD_3 ganglioside is BEC-2 (Mitumomab; ImClone Systems) (323). An international randomized Phase III trial is being conducted to evaluate BEC-2 plus BCG as adjuvant therapy after chemotherapy and irradiation in limited SCLC. In North America, a bivalent ganglioside vaccine, MGV (Bristol-Myers Squibb), is under study at the Phase II level. If results are promising, a Phase III trial will be undertaken. Another attempt at immunomodulation involves the use of *Mycobacterium vaccae* (SRL172) given as a monthly intradermal injection in newly diagnosed patients with inoperable NSCLC and mesothelioma. Results from a Phase II trial showed a tendency toward a better response in patients who received SLR172 compared with those who received chemotherapy alone (324). A Phase III study is now in progress.

CONCLUSION

Progress in lung cancer remains painfully slow, despite a sustained interest in both basic biological research and clinical trials.

Better understanding of genetic predispositions to contracting the disease may identify the smoker at greatest risk. Screening looks promising, but expensive and needs to be assessed carefully and patiently. Although improved detection of occult disease at staging for possible surgery looks likely to be greatly advanced with PET scanning, it is a "negative" step as it will prevent rather than increase the resection rate.

In the field of radiotherapy, hyperfractionation techniques hold promise for those with localized but unresectable disease, and chemotherapy–irradiation for this group and those with more advanced disease appears a modest step forward.

Although chemotherapy in SCLC is not notably advancing, its role in NSCLC is becoming better defined. Neoadjuvant chemotherapy may find a place before resection for Stage I and II disease. Its place for the huge number of sufferers with advanced disease is limited to those with better performance status, and provides a small extension to survival with quality of life issues still under debate.

The next decade will be one of screening trials for early disease, how to manage carcinoma *in situ*, and the assessment of the plethora of biological growth-modifying agents, either with or in place of chemotherapy.

No review such as this should close without a plea for tougher legislation worldwide against tobacco.

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