Lung cancer—areas of progress

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Lung cancer remains the most common cause of death due to malignancy in the western world accounting for approximately 25,000 deaths in the United Kingdom and 120,000 in the United States of America in 1981. This article examines some areas of recent interest and where possible progress is being made in the prevention, detection and treatment of this disease.

Epidemiology

Since the major factor controlling the incidence of lung cancer is smoking, future trends will depend on what happens to smoking habits during the next decade. Although deaths due to lung cancer have been increasing steadily since the First World War in parallel to the increasing consumption of tobacco, there have been changes in these trends recently. During the last few years, deaths in men have stabilized and are now beginning to fall, whilst in women the death rate is rising sharply. Ten years ago a sex incidence of 10 men to one woman was usual, now it is two-three to one. This change is entirely consistent with the increased smoking habits of women. The decline in male mortality is occurring earlier than might be expected from changes in smoking habits alone, and geographical, occupational and environmental factors appear to be important additional reasons.

The mortality in different countries varies widely even when smoking habits are taken into account. For example, the U.K. and Germany fare worse than France and Italy. It seems likely that heavy industry and coal burning have been important. The legislation for cleaner air has seen a dramatic fall in environmental and occupational pollution in the last two decades, and almost certainly preceding significant changes in smoking habits. Thus there is a cohort of people passing through the population who have both smoked and breathed polluted air for many years. These people have a very greatly increased risk of lung cancer, but with today's cleaner air, the younger smoker has a lower risk. This would account for the clustering of cases in the older

population and the falling age specific death rates in the under 60s.

Detailed studies of some specific occupational pollutants also give a clear message. For example, asbestos exposure acts in synergy with cigarette smoking to give an 80-90-fold increased risk for dual exposure, compared to 10-20-fold risks of smoking alone (Selikoff, Hammond and Chung, 1968). In some countries it has become illegal to employ a cigarette smoker as an asbestos worker.

Trends in tobacco consumption

The impact of anti-smoking propaganda has led to significant changes in tobacco consumption in many European countries, the United States of America and Australia. However, those committed to the anti-smoking cause continue to stress that in the United Kingdom only the basic minimum is being done, and the finance given to health education represents a tiny percentage of the income of the tobacco processors. Nevertheless, cigarette consumption has been falling since 1975 and many smokers have switched to 'safer' tobacco products. The proportion of regular smokers in the population has been falling steadily in men since 1972 and is now stable in women. Also the anti-smoking propaganda has affected upper social classes more where only 21% of professional workers are smokers, than the lower social classes where 57% of unskilled manual workers continue to smoke.

Screening

One of the most disappointing aspects of lung cancer is that efforts to detect the disease sufficiently early to affect the outcome by routine screening of the population at risk have been far less rewarding than in some other cancers. The important conclusions can be drawn from two very comprehensive recent studies.

The Philadelphia Pulmonary Neoplasm Project (Weiss, Boucot and Seidman, 1982) involved screening 6136 men enrolled between 1951 and 1955 with 6-

monthly chest X-rays for 10 years. There were 121 incidence cases and in these survival was only 8% at 5 years, similar to the U.S. national figures for unscreened patients. Only 19 of the 121 cases were considered ideal candidates for surgery.

The Mayo Lung Project (Woolner *et al.*, 1981) has yet to be finally reported. It is a randomly controlled study employing routine radiological screening and sputum cytology. This has shown that regular sputum cytological examination adds little to radiological screening. The 5-year survival in the close surveillance group was superior to the control group—a reflection on the earlier diagnosis or 'lead time' of the screened group—but the mortality has not improved.

The staging of lung cancer

Systematic recording of tumour distribution at diagnosis was applied to lung cancer only as recently as 1974 when the American Joint Committee for Cancer Staging and End Results Reporting applied the Tumour-Nodal Involvement-Metastases (TNM) system. The initial report on 2,000 cases by Mountain *et al.* (1974) showed the advantages of the TNM staging to prognosis in squamous, adeno and large cell cancers but not for small cell. The failure to predict favourable groups in patients with small cell cancer of the bronchus (SCCB) is primarily due to the propensity for this cell type to grow rapidly and disseminate early and widely. Thus clinical and biochemical tests together with radioisotope scans were too insensitive to identify nodal and metastatic spread. Small cell lung cancer is now generally regarded as an inoperable disease due to its disseminated nature at diagnosis. The same problem of metastatic spread exists in non-small-cell histological types but affects staging less obviously because of the slower growth rates of non-small-cell lung cancers and their lower tendency for widespread dissemination.

Application of the TNM staging system to non-small-cell lung cancer eliminates up to 70% of cases from possible surgery. Of those undergoing resection thought to be curative up to 75% may relapse within 5 years due to occult metastases present at the time of surgery. Clearly the incidence of relapse is less in T1 N0 tumours than T2 N1 lesions, but is still due to failure to identify small metastases. Considerable difficulty still exists in combating this problem.

Mediastinoscopy

Mediastinoscopy has helped to identify patients with mediastinal lymph node involvement despite normal PA and lateral chest X-rays—almost 50% of potentially operable patients with no mediastinal widening on chest X-ray have mediastinal nodal

involvement (Whitcomb *et al.*, 1976). Accepting the criterion that mediastinal node involvement renders a tumour inoperable, about 20% of patients with non-small-cell lung cancer are spared a thoracotomy by staging mediastinoscopy.

A recent study illustrates well the benefit of mediastinoscopy. Of 874 patients considered to be operable candidates, 236 (27%) were found to have involved lymph nodes at mediastinoscopy and not treated surgically; 79% of these died within 1 year. Of those with a negative mediastinoscopy 97% (638 patients) were resectable with a 5-year survival of 24.5% (Ashraf, Milsom and Walesby, 1980).

In particular a high yield from mediastinoscopy has been demonstrated with central tumours of all cell types and with poorly differentiated peripheral tumours (Hutchinson and Mills, 1976; Whitcomb *et al.*, 1976). However, even with well-differentiated peripheral tumours, the size and site is not an adequate criterion to forego a staging mediastinoscopy.

Non-invasive staging of the mediastinum

The increased availability of computed tomography (CT) scanning has had a major effect on the T and N staging of lung cancer. Computed tomography scans of the thorax provide a clearer delineation of the tumour mass, the TNM status may be downgraded in up to 40% of non-small-cell patients and 55% of small-cell cancers. However, the demonstration of enlarged mediastinal lymph nodes on CT scans should not automatically lead to the conclusion they are infiltrated by tumour. Glands excised at removal of T1 and T2 tumours are frequently enlarged and show reactive hyperplasia. Initial studies comparing CT to biopsy results in the mediastinum reported a CT scan false negative rate of 28% (Underwood *et al.*, 1979). However, later studies report lower false negative rates—2 out of 51 (Faling *et al.*, 1981), 1 out of 22 (Rea, Shevland and House, 1981). A normal CT scan of the mediastinum can exclude the necessity of mediastinoscopy and the surgeon should proceed directly to thoracotomy. However, a positive CT scan of the mediastinum should not necessarily be interpreted as inoperability. In 23 of 44 patients studied by Goldstraw, Kurzer and Edwards (1983) there was some abnormality seen on CT in the mediastinum. In 12 the mediastinum was abnormal but in the remaining 11 resection was possible in nine with six cases being N0, two were N0 with a minor degree of mediastinal invasion not preventing resection, and one was N1 without mediastinal invasion. Thus although CT has improved the definition of the mediastinal structures, and the exact delineation of the tumour and its relationship both to the mediastinum, the pleura and

the chest wall, a positive finding in the mediastinum should still be confirmed.

Another non-invasive technique for mediastinal staging is to use tumour-seeking isotopes. Clinical experience has been limited to gallium-67 in particular, and also ^{57}Co labelled bleomycin.

Most studies report an incidence of 80–90% of accumulation of the isotopes in primary lung cancers. However, the uptake of neither isotope is specific to neoplasms, but occurs also with inflammatory lesions (tuberculosis, sarcoidosis, pneumonia) and metastases. However, in practice the lack of specificity is rarely a problem.

The accuracy of gallium-67 in identifying mediastinal disease is similar in several studies—in the region of 80% (Alazraki *et al.*, 1978; De Meester *et al.*, 1976; Lunia *et al.*, 1981) and more sensitive and accurate than the plain chest radiograph. Its accuracy in demonstrating mediastinal lymph node involvement is comparable to CT scanning. However, as with CT, gallium-67 cannot detect malignant nodes smaller than 1.5 cm. A disadvantage of gallium-67 in comparison to CT is that whilst CT is an excellent technique for identifying direct mediastinal invasion by tumour, this cannot be done with gallium-67. Thus in patients with primary paramediastinal tumours gallium uptake by adjacent mediastinal nodes may not be separately identifiable, and central tumours which invade the hilum or mediastinal tissues directly cannot have their anatomy as clearly defined as with CT.

Combined results show the predictive values of positive and negative scans are roughly equal. However, most regard the positive gallium scan as an indication for mediastinoscopy. Only de Meester *et al.* (1979) suggest on the basis of a 90% probability that a positive scan indicates inoperable disease and preclude the need for confirmatory mediastinoscopy.

The clinical significance of a negative gallium scan (provided the primary tumour takes up the isotope) is also not completely clear cut, with contrasting advice from different studies. However, most claim a predictive value of 75–100% for a negative mediastinal scan and therefore suggest proceeding direct to thoracotomy (Alazraki *et al.*, 1978; Lunia *et al.*, 1981).

Extrathoracic metastases

Little advance has been made in the detection of small extra thoracic metastases. Although CT body scanning (including brain) may identify a few lesions not visible on radioisotope or ultrasound scans, their expense and general non-availability far outweighs this small advantage. Brain and liver scans in patients with lung cancer and no specific symptoms referable to these organs do not warrant specific isotope examination. Bone scanning is notorious for its false

positive lesions and remains an open and unsatisfactory area.

Results of treatment of non-small-cell lung cancer (NSCLC)

Surgery

Approximately 20–30% of all patients presenting with NSCLC will undergo thoracotomy after staging. Of these 1–5 patients will still be unresectable despite a negative mediastinoscopy. This is due to nodal involvement beyond the range of the mediastinoscope or tumour invading vital structures. Thus about 20% of all patients will undergo a 'curative' resection of which four to five will be alive and tumour free at 5 years—a 25% 5-year survival rate overall for this selected group of resected subjects. The other patients will die of local or distant recurrence within 5 years. The overall 5-year survival figure of 20–30% and 16–18% 10-year survival (there is a significant fall off between 5 and 10 years due to metastatic spread from slowly growing lung cancers) has not changed during the last 30 years. These figures can however be somewhat misleading as they will include 40–50% of patients with stage I disease. In these the 5-year survival is much greater, 55–70%, particularly for squamous cell carcinoma.

Adjuvant therapy

The poor overall results of surgery have led to many studies of adjuvant therapy including chemotherapy, radiotherapy and more recently, immunotherapy. Many studies published to date have not given adequate details of staging and this has made interpretation of results extremely difficult. Adjuvant therapy must be safe and toxicity acceptably low as some patients, especially those with Stage I tumours, may already have been cured by their operation.

Immunotherapy. During the last 6 years many studies have investigated an immunological approach to surgical adjuvant therapy. This follows the observation that patients developing postoperative empyemata had lower relapse rates than those with an uncomplicated postoperative course, and the study of McKneally, Maver and Kausel (1977) using intrapleural instillation of Tice BCG. At a follow-up of 2 years, McKneally *et al.* found that the immunotherapy treated group with Stage I disease had 93% of cases disease free, compared with 67% of controls. There was no benefit in patients with Stage II or III disease. Other methods of administering BCG—subdermal, scarification or interdermal—have failed to show any benefit in preventing relapse.

Levamisole, an antihelminthic drug, alters T cell function and has been given orally as an immuno-

stimulant. There has been no evidence of clear efficacy, and shorter survival in the treated patients with an excess of deaths due to cardiorespiratory causes, tentatively related to the drug, has been reported.

Another agent, *Corynebacterium parvum*, was claimed to give encouraging results when given intravenously or subcutaneously (Israel *et al.*, 1975). However many subsequent studies have proved disappointing and the injection of the organism, particularly by the intravenous route, is associated with a high incidence of side effects including fever, pain and malaise for several hours.

It would appear that the likelihood of immunotherapy fulfilling its earlier promise is small, but the possibility remains that benefit may accrue for Stage I tumours and this is likely to be answered by the large studies currently in progress evaluating intrapleural BCG.

Radiotherapy. Several studies of pre-operative radiotherapy have failed to show that it prolongs survival (Shields *et al.*, 1970; Warram, 1975). Pre-operative radiotherapy is however still advocated for superior sulcus tumours provided the mediastinal structures are not involved, although a 40% 5-year survival is possible by surgery alone.

Surprisingly the role of postoperative radiotherapy is still not clear. This is due to inadequate information on staging and whether resections were considered 'curative' or not. Two recent studies advocating postoperative radiotherapy for patients with mediastinal and hilar node involvement are uncontrolled (Green *et al.*, 1975; Kirsch and Rotman, 1976). In the study of Kirsch and Rotman, the 5-year survival of patients with squamous cell cancer undergoing radiotherapy with mediastinal metastases was 34% compared to 53% 5-year survival for N0 M0 disease. With adenocarcinoma, none of the patients who received radiotherapy for hilar nodal involvement survived 5 years, and 12% with mediastinal nodes were disease free at 5 years. Controlled studies are important in this area.

Chemotherapy. No benefit of single or multiple drug chemotherapy has ever been shown. The largest review by Selawry (1976) of single and multiple drug trials were all negative. Other studies highlighted the toxicity of chemotherapy and other single agent studies have shown a significant shortening of survival.

Radiotherapy

In patients with a resectable tumour in whom an operation is not performed, treatment with radiotherapy is less effective than surgery. The best survival figures for radiotherapy in apparently operable lung cancer are those of Smart and Hilton (1956) in which

very carefully planned treatment was given to 40 patients mainly suffering from squamous cell tumours. They received up to 5,000 rads in 6 or 7 weeks with a 23% 5-year and 8% 10-year survival. This study was not controlled and a randomized study of surgery or radiotherapy (Morrison, Deeley and Cleland, 1963) showed inferior results with a post-radiotherapy 4-year survival of 8% compared with 30% following surgery. Although the optimal dose for radiotherapy remains controversial there is little evidence that radiotherapy to localized lung cancers significantly increases the 5-year survival rate beyond 4-9%, marginally better than no treatment. In a trial of radiotherapy against no specific treatment to inoperable patients with disease confined to one hemithorax the survival figures at 1 year were marginally superior for radiotherapy, particularly in squamous cancers, but the differences were not significant (Roswitt *et al.*, 1968). Better results were obtained by Guttman (1971) in similarly localized inoperable patients with squamous cell carcinoma—a 57% 1-year and 8.7% 5-year survival. However, despite short-term improvement in survival described by some with radiotherapy for inoperable localized disease, the number of patients shown to be cured remains small.

Radiotherapy is however an excellent palliative treatment for symptoms such as recurrent haemoptysis, pneumonia distal to an obstructed large airway, superior vena caval obstruction, bone pain and cerebral metastases.

Cytotoxic chemotherapy

Over 50% of patients with NSCLC present with evidence of metastatic disease, and metastases will develop in many others following failure of initial treatment to control the disease. Whilst chemotherapy has produced modest advances in the management of small cell carcinoma of the bronchus this is not true for other cell types. The clinician is however becoming increasingly pressurized to treat his patients with cytotoxic chemotherapy. There have been more than 200 studies of chemotherapy for inoperable advanced NSCLC but evidence for a worthwhile prolongation of survival, or indeed any evidence that this situation will change in the near future is completely lacking. The lack of progress and sheer numbers of patients with advanced NSCLC can easily lead to nihilistic attitudes to treatment.

Single agents produced a response rate (i.e. at least a 50% reduction in tumour diameter) in the region of 10%, and combinations of cytotoxic drugs may result in a larger percentage of 'responders'. However, a response to chemotherapy does not equate simply to a prolongation of survival. The majority of reported studies do not contain a randomized prospective

control group and either compare their data to retrospective control subjects or compare responders to non-responders. The latter is open to strong criticism as non-responder cases often have more advanced disease or poorer general health, or low performance status. Response rates with combination chemotherapy of 2–4 drugs are not much higher than with single agents. Most of the studies contain too few patients especially when analyzed according to cell type. Although partial regression of tumour by chemotherapy is relatively common a complete response is very occasional indeed. As yet the case for cytotoxic chemotherapy in non-small-cell lung cancer is not made and should be considered a subject for careful future clinical studies. Newer agents should be carefully assessed by clinical trial—and currently agents such as cisplatin, vindesine, ifosfamide have shown some activity but are unlikely to provide a major survival advantage.

Laser therapy

In view of the side effects associated with radiotherapy and combination cytotoxic chemotherapy and the propensity for lung cancers to relapse at the primary site, the advent of local treatment to eliminate endobronchial tumour has been of much interest. The patients most suitable for palliation by laser therapy are those with endobronchial tumour in the trachea, carina, or main bronchi and also with significant symptoms such as dyspnoea, stridor, recurrent lobar/lung collapse or haemoptysis. The laser beam in effect burns away endobronchial tumour. The beam is conducted down a quartz-fibre passed through the suction channel of a fiberoptic bronchoscope, or used in conjunction with a rigid bronchoscope. The beam can be directed with great precision to the treated area which undergoes photo-coagulation and subsequent necrosis. Sometimes several sessions are required for maximal effect.

Preliminary results with laser therapy show it to be effective in controlling haemoptysis, effective at relieving upper airways obstruction, and in re-expanding collapsed areas of lung. However, in the latter situation fulminating infections have occurred perhaps due to aspiration of the trapped contents distal to the blockage (Hetzel *et al.*, 1983).

A more promising approach is the combination of laser treatment with the injection of a light sensitive material haematoporphyrin D. This is preferentially concentrated in some of the tumour cells causing selective photosensitization. A dye laser using light of the appropriate wave length is then applied to the tumour, hopefully causing more extensive and specific damage to the tumour mass.

Laser treatment is likely to be of value in selected

patients but it is at best of limited value and will make little impact overall on lung cancer.

Small-cell carcinoma of the bronchus (SCCB)

This cell type accounting for 20–25% of all lung cancers differs from the other lung cancers in being disseminated from its outset—the main reason for no relationship being established between clinical disease stage and survival.

Cell biology

During the last 5 years there have been some advances in understanding the biology of SCCB. Tissue culture techniques have confirmed the earlier circumstantial evidence that the disease arose from Kulchitsky cell type (K cell), of the amine precursor uptake and decarboxylase (APUD) system. The cell of origin is now considered to be the granulated basal lining cell (K cell) of the bronchial mucosa and completely different origin to the other cell types of lung cancer. The tissue culture systems which have confirmed the APUD nature of SCCB (Gazdar *et al.*, 1980; Pettengil, Sorenson and Wurster-Hill, 1980) have also produced continuous clonable cell lines which maintain APUD characteristics including high levels of neurone-specific enolase, dopa decarboxylase and bombesin. These systems may help provide a better understanding of growth control mechanisms involved in this disease and a better definition of specific chromosomal abnormalities associated with malignant process. Samples of individual tumours can also be grown in culture and the sensitivity of the tumour to individual cytotoxic drugs assessed. Another process based on xenografting tumour cells from individual patients on to irradiated nude mice is too slow to help the individual patient, but the *in vitro* and *in vivo* responses are similar and have built up information on the efficacy of cytotoxic agents. Human tumour colony forming assays have recently been used to predict the clinical response accurately in some tumours, but not yet in SCCB. However, it is a promising and growing field, capable of examining tumour susceptibility and resistance and the nature of resistance to individual cytotoxic drugs in SCCB (Curt *et al.*, 1983).

Histology

The histological diversity of SCCB has been long recognized. Recently the effects on prognosis have become more apparent, particularly in those cases of 'mixed' histology with both small and large cell components present at diagnosis. These mixed tumours respond less well than 'pure' tumours to chemotherapy, and their overall survival despite treatment is significantly less (Radice *et al.*, 1982).

Treatment of SCCB

Much of today's interest in SCCB is due to the tumours considerable, but often short-lived, responsiveness to several cytotoxic agents—in particular cyclophosphamide, epipodophyllotoxin, methotrexate, adriamycin, vincristine and vindesine. Using combinations of three or four cytotoxic agents the median survival has increased from about 2–4 months in untreated patients to 12–18 months overall. However, in patients staged to have limited disease (tumour confined to one hemithorax including the ipsilateral supraclavicular fossa) the median survival is in the region of 18 months, and for extensive disease is about 9 months.

Patients with limited disease stand the best chance of a prolonged survival and the achievement of a clinical complete response (no *evaluable* disease) remains the most important prognostic factor. Most patients with limited disease have been treated with combination cytotoxic chemotherapy and also irradiation to the primary tumour site and the mediastinum at some stage. The best results to date record a 23% rate of patients free of detectable disease at two years or more after starting treatment (Greco and Oldham, 1979). However, most studies fall short of this and a plateau has now been reached in the survival of SCCB to combination cytotoxic chemotherapy. Using different combinations of cytotoxic agents the median survival data is not improving. Our own data examining the specific effects of adding mediastinal irradiation to combination chemotherapy in both limited disease and extensive disease patients has as yet failed to show an advantage for the addition of radiotherapy to survival, although the relapse rate at the primary site is somewhat reduced. This also serves to emphasize that the failure to control the disease is primarily a failure of chemotherapy to eradicate disseminated tumour. This is either due to tumour developing resistance to chemotherapy, or to the emergence of an original resistant cell line which becomes the dominant stem cell after the death of stem cells sensitive to chemotherapy. The failure to regain control in relapsed disease, even using drugs not previously given to the patient adds to the concept that SCCB breaks through treatment because not all its malignant cells are sensitive to chemotherapy. Thus in time the resistance cell clone becomes dominant and kills the patient.

In view of the disappointing progress in recent years alternative methods in administering established agents have been evaluated.

High dose chemotherapy. Animal studies have shown that the cytotoxic effect of cyclophosphamide increases with dosages much higher than those conventionally given to man. The dose limitation

with cyclophosphamide—bone marrow depression and haemorrhagic cystitis, can now be avoided by autologous bone marrow replacement and by mesna (2-mercaptoethane sulphonate) which binds to acrolein, the waste product of cyclophosphamide metabolism that is responsible for the haemorrhagic cystitis.

High dose treatment with cyclophosphamide is currently being investigated in SCCB (Souhami *et al.*, 1982). 150–200 mg/kg (approximately 10 times the conventional dose) has been given to patients with limited disease SCCB. The patients received mesna during drug administration and have their bone marrow harvested prior to therapy and returned 2–6 days after chemotherapy is complete. Subsequent treatment has included radiotherapy (4,000 r) to the primary site and mediastinum. Following a single high dose course of cyclophosphamide 16 of 25 patients achieved a complete response and the median duration of remission off all treatment was 49 weeks with a median survival of 66 weeks. These results compare very favourably with other treatments and has the advantage of a single relatively short spell in hospital. Side effects were surprisingly few. This pilot study is encouraging in three ways. First it demonstrates that even with a well-established drug there is much to be learned about the dose schedule and the response possible. Secondly, it raises the possibility of reducing the number of treatment courses to achieve a desired effect. In view of the unfavourable adverse effects of prolonged cancer chemotherapy this is highly desirable. Finally it allows cautious hope that more intensive chemotherapy might bring long-term cure in a selected group of patients with this disease. Further work is now in progress to intensify the drug regimen and explore whether marrow replacement is really necessary.

Another conventional treatment currently being re-evaluated is radiotherapy—given as whole-body irradiation. Small-cell carcinoma of the bronchus is a highly radiosensitive tumour. However, conventional radiotherapy is limited in its effect as it is a local therapy for a disseminated disease. Hence interest in giving radiotherapy to the whole body to control micro-metastases has evolved. However, early results comparing total irradiation to combination chemotherapy has shown no real advantage with a three drug combination regimen having considerable advantage for those with advanced disease (Urtason *et al.*, 1982).

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