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Editorial

The staging of lung cancer

Although the overall cure rate for lung cancer is not improving it has become increasingly recognised over the last 10 years that accurate subclassification of tumour cell types and determining the extent of the disease at presentation are the two most important steps that allow treatment decisions to be made. The need for precise classification of the anatomical extent or stage of lung cancers led to the application of the tumour nodal involvement metastasis (TNM) system to this disease in 1973 (table). The first report on 2000 cases studied by the American Task Force for Lung Cancer[1] showed that the anatomical stage of lung cancer at presentation clearly influenced prognosis in squamous and large cell tumours and adenocarcinomas. The size of the tumour, whether it was peripheral in the lung, and the presence or absence of evidence of nodal spread were the most important factors. The natural history of squamous cell cancers was more favourable than that of adenocarcinoma, which was in turn more favourable than that of large cell tumours when they were matched for stage. Small cell lung cancers formed an entirely different category as no staging grade had any apparent influence on survival. The propensity of this cell type to disseminate early is such that it has now come to be regarded as disseminated at presentation, and is treated systemically by cytotoxic chemotherapy in all but a tiny proportion of cases. This editorial evaluates the investigations currently available for staging lung cancer and suggests which tests should be carried out and when.

Staging of non-small cell cancer

The prognosis of squamous cell carcinoma, adenocarcinoma, and large cell cancers (that is, non-small cell lung cancers) depends heavily on successful surgical intervention. The introduction of the TNM staging system has encouraged an ordered assessment for selecting those cases most suitable for surgery; it has improved the rate of resection and should result in an improvement over the present five year survival of 25% and the 10 year survival of 16–18% for all operated cases.[2–5] Most will agree that stage I and stage II patients (table) should be operated on, and that stage III disease is inoperable. The emphasis in preoperative staging must therefore be to assess those factors that cause a neoplasm to become stage III—that is, T3, N2, and/or M1. Not all surgeons, however, as yet undertake routine preoperative staging and the average survival data are downgraded by subjecting patients with a poor prognosis to surgery. Careful staging prevents the distress of unnecessary thoracotomy for incurable patients.

At the time of diagnosis up to two thirds of

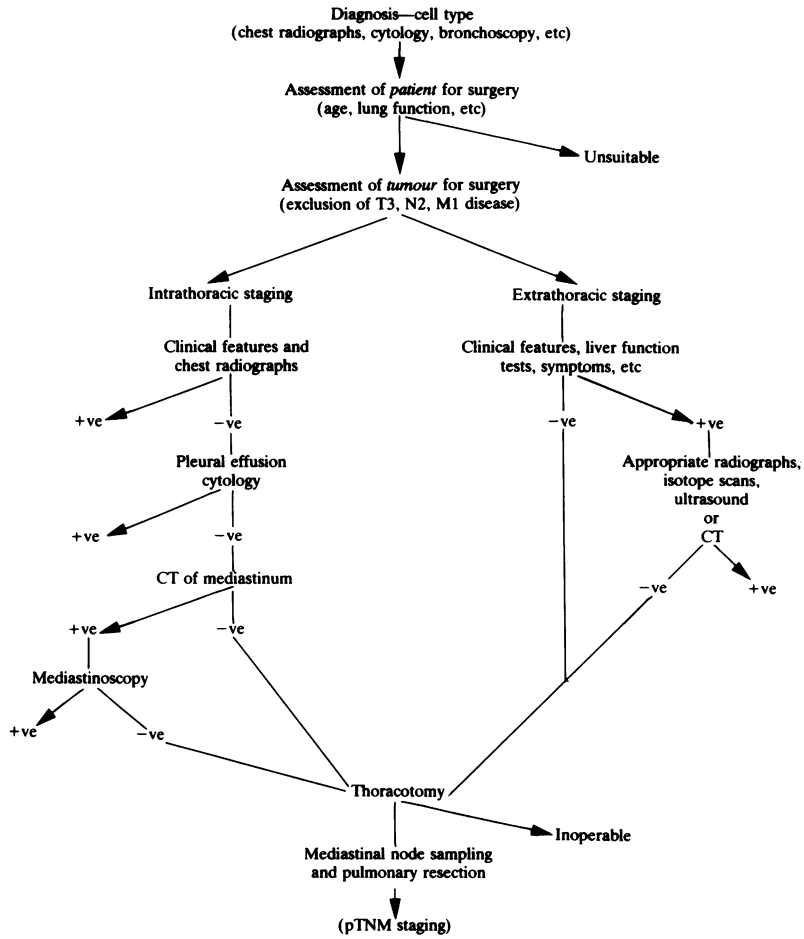
Definitions for staging bronchogenic carcinoma (American Joint Committee on Cancer Staging, 1973)

T0:	No evidence of primary tumour
TX:	Tumour proved by the presence of malignant cells in bronchopulmonary secretions but not visualised roentgenographically or bronchoscopically, or any tumour that cannot be assessed
TIS:	Carcinoma in situ
T1:	A tumour that is 3·0 cm or less in greatest diameter, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy
T2:	A tumour more than 3·0 cm in greatest diameter, or a tumour of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumour must be within a lobar bronchus or at least 2·0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung, and there must be no pleural effusion
T3:	A tumour of any size with direct extension into an adjacent structure such as the parietal pleura or chest wall, the diaphragm, or the mediastinum and its contents, or a tumour demonstrable bronchoscopically to involve a main bronchus less than 2·0 cm distal to the carina; or any tumour associated with atelectasis or obstructive pneumonitis of an entire lung or pleural effusion
N0:	No demonstrable metastasis to regional lymph nodes
N1:	Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension
N2:	Metastasis to lymph nodes in the mediastinum
M0:	No (known) distant metastasis
M1:	Distant metastasis such as in scalene cervical or contralateral hilar lymph nodes, brain, bones, liver, or contralateral lung

SUMMARY OF STAGING

Stage I (operable)	T1	N0	M0
	T1	N1	M0
	T2	N0	M0
Stage II (operable)	T2	N1	M0
Stage III (inoperable)	T3	any N	or M
	N2	any T	or M
	M1	any T	or N

Address for reprint requests: Dr Stephen G Spiro, Brompton Hospital, London SW3 6HP.



Preoperative staging of non-small cell lung cancer. +ve—positive; −ve—negative; CT—computed tomography; pTNM staging—ie post surgical treatment–pathological staging.

patients are found to be inoperable. Often this is obvious immediately because of one or more of such factors as age and general health, poor lung function, or extrathoracic disease. The diagnosis of lung cancer and the assessment of a patient for surgery is beyond the scope of this article. Assessment of the suitability of a tumour for resection (illustrated in the form of a flow chart in the figure) can most simply be divided into its intrathoracic and extrathoracic components. Although these are assessed in parallel we will consider them separately. As intrathoracic staging frequently culminates in surgical exploration we will discuss extrathoracic staging first.

EXTRATHORACIC STAGING

Patients with non-small cell cancer considered operable after clinical examination, chest radiography, and bronchoscopy, with no symptoms other than those caused by the primary tumour, in many cases fail to be cured after mediastinoscopy and thoracotomy because of extrathoracic metastatic disease. The results of isotope scans of brain and liver with technetium 99m or radiolabelled albumin are usually normal in subjects without either organ specific or non-specific features (weight loss, anaemia, abnormal biochemistry, etc) to suggest occult metastases.[6,7] Bone scanning, which frequently yields positive results in patients with symptoms,[6] has been widely criticised for its lack of specificity, up to 40% of scans being falsely positive.[7] Patients who are apparently operable and who have no symptoms other than those of the primary tumour are likely to have truly positive bone scans in

under 4% of cases and those with no musculoskeletal symptoms are not recommended to have scans.[6 7] Recommending the paradoxical step of abandoning isotope scanning in patients with neither organ specific nor non-specific symptoms is based on the insensitivity of the test rather than the likelihood that the tumour will not have disseminated.

Gallium-67 has also been used for whole body staging but appears no more sensitive than conventional isotopes. Follow up data on the number of occult metastases missed by routine isotope scanning in symptom free subjects who undergo resection are not available.

Studies are currently in progress to evaluate the sensitivity of computed tomography in identifying occult extrathoracic disease (Goldstraw *et al*, unpublished data). Modini *et al*[8] found 24 instances of asymptomatic metastases with computed tomography scans of brain and upper abdomen in 85 patients (including 24 with small cell cancers) considered operable. Deposits were identified in the brain (10 patients), liver (8), adrenals (7), bone (6), retrocrural nodes (4), and spleen (2). Only 10 cases were proved by biopsy.

Other studies in progress suggest an incidence of about 10% for asymptomatic cerebral deposits in patients with non-small cell lung cancer being assessed for surgery—but most of these had other asymptomatic metastases in the mediastinum (most commonly) and abdomen, suggesting that the additional computed tomography brain scan would identify an isolated metastasis in only 2–3% of all cases. No comparison of the sensitivity of computed tomography and of isotope scanning is available but computed tomography would appear to be superior. Ultrasonic investigation, especially of the liver, is only marginally better than isotope scanning, and not as effective as computed tomography. Most studies comparing the sensitivity of all three techniques have been concerned with other types of malignant disease, but there appears to be no reason why these evaluations should differ in metastatic lung cancer.

INTRATHORACIC STAGING

Initial clinical assessment will identify obvious mediastinal disease causing superior vena caval obstruction, dysphagia, etc. Pleural effusions have to be investigated for the presence or absence of malignant cells to decide whether the effusion is due to direct spread of the primary tumour to the pleura. In those patients who have tumours considered operable on bronchoscopic grounds and who have no radiological evidence of contraindications to surgery the exact role of mediastinal staging in deciding whether a patient should undergo resection has proved to be a subject of considerable controversy.

For patients whose chest radiograph shows obvious mediastinal lymphadenopathy there is no prospect of curative surgery. Routine preoperative mediastinal exploration identifies a considerable number of patients who have mediastinal disease (N2 stage) that was not visible on posteroanterior or lateral chest radiographs. Since its introduction by Carlens in 1959 mediastinoscopy has been shown to have a very low morbidity rate yet it is not universally accepted as a preoperative staging procedure. Typical recent results for patients with a normal mediastinal appearance on chest radiographs show that there are positive findings at mediastinoscopy in about 25% of cases.[9 10] Of those patients who did not undergo resection as a result of mediastinoscopy, 79% died within one year. Pulmonary resection was possible for 97% of the patients without mediastinal disease, with a five year survival of 25%.[9]

The site, size, and cell type of the tumour also influence the likelihood that mediastinoscopy will show disease. For well differentiated peripheral tumours of less than 3 cm there is a very low incidence of mediastinal disease, while for undifferentiated tumours, larger masses, or central lesions visible at bronchoscopy the incidence of positive mediastinal lymph nodes at biopsy, despite no mediastinal abnormality visible on chest radiographs, is up to 50%. Thus with a well differentiated non-small cell tumour of less than 3 cm one may proceed direct to thoracotomy provided that the chest radiograph shows no mediastinal abnormality. Larger tumours or central lesions should, however, have mediastinal exploration whatever the cell type and degree of differentiation.

For most lesions mediastinal exploration is best undertaken by cervical mediastinoscopy, which allows assessment of both paratracheal chains and a limited examination of the main carinal nodes. Left upper lobe tumours require special consideration, however, as the lymphatic drainage is affected by the presence of the aortic arch and tumours within that lobe can affect anterior mediastinal, paraaortic, and other gland groups in the subaortic fossa that are not easily accessible by mediastinoscopy. It has been shown[11 12] that the staging of left upper lobe tumours is improved if mediastinoscopy is supplemented by left anterior mediastinotomy. This is an extrapleural approach to the subaortic fossa through an incision in the left second intercostal space.

Pearson[13] noted a wide range of survival rates in series of patients with positive findings at mediastinoscopy, ranging from nil to 29% at five years, the higher rates coming from uncontrolled studies that

included preoperative radiotherapy.[14 15] A similar range of survival rates is reported for those patients whose mediastinal disease became apparent only at thoracotomy, after negative findings at mediastinoscopy: five year survival rates have ranged from nil to 41% with or without adjuvant radiotherapy or chemotherapy.[16] There is, however, considerable difficulty in interpreting these data owing to lack of precision in reporting the sites of mediastinal node disease at thoracotomy and whether the metastatic disease was macroscopic or microscopic. The results of these studies on surgical series strengthen the case for precise anatomical staging of the mediastinal node stations at thoracotomy if we are to attempt to identify particular sites that may be affected within the mediastinum, but they do not necessarily represent an absolute criterion of inoperability. A recent statement by the American Thoracic Society[17] draws attention to the variability in the reporting of surgical results for patients with N2 disease and suggests guidelines for detailed mediastinal lymph node mapping to identify the more favourable prognostic factors as an alternative to the polarised approach to mediastinal disease that is prevalent.

Pearson *et al*[16] have proposed some guidelines for identifying "favourable" factors in positive mediastinoscopy findings. After excluding the great majority of patients with mediastinal disease from surgery (those with superior mediastinal node disease, contralateral spread, extracapsular spread, or fixation to mediastinal structures), they proceeded to thoracotomy in a small group of patients with ipsilateral node disease in low paratracheal glands or in tracheobronchial or anterior subcarinal glands or both, but they achieved only a 9% five year survival rate overall. By contrast, another group of 62 patients with negative mediastinoscopy findings who were subsequently found to have metastatic disease in the mediastinum at thoracotomy achieved a five year survival rate of 24%, with a considerable advantage for squamous cell cancers. These results are made harder to interpret because preoperative or postoperative irradiation was used in a considerable number of the patients, but there seemed no obvious advantage in the addition of radiotherapy.

Clearly the general application of mediastinal exploration as a preoperative staging investigation will prevent unnecessary thoracotomies, and it is hoped that careful nodal mapping both at mediastinoscopy and at thoracotomy will be performed in future studies to settle the question of whether patients with any mediastinal disease should have a pulmonary resection and if so which patients.

Non-invasive assessment of the mediastinum

The recent advances in non-invasive diagnostic imaging, such as computed tomography, have been used to assess whether they might take the place of mediastinoscopy with consequent saving of theatre time, morbidity, and so on. Computed tomography has a clear advantage over plain radiography[18–20] and conventional tomography[20 21] in the detection of mediastinal lymphadenopathy.

Several studies have compared computed tomography staging of the mediastinum with mediastinoscopy and postsurgical staging. Studies using the first generation of computed tomography scanners with scanning times of 18–20 seconds found a low sensitivity in detecting mediastinal adenopathy—44%,[22] 50%,[8] 77%,[23] and 75%.[24] With the use of newer models with a scanning time of 2–3 seconds the sensitivity has improved to 80%[24]—94%.[20]

The decision as to whether a node is abnormal or not is an arbitrary one based on size, most reports assuming a 1·5 cm diameter as the upper limit of normal. Nodes may, however, enlarge owing to reactive hyperplasia or previous inflammatory change (for example, that of tuberculosis) and may cause false positive scans. Not surprisingly therefore the resultant specificity (true negative/true negative + false positive) of computed tomography has varied from 94%,[18] with only two false positive mediastinal scans in 51 examinations, to 63%,[20] with 9/24 false positive scans. Another common cause for false positive results is associated atelectasis, causing the margins of the lung and mediastinum to become difficult to identify with computed tomography. In general, computed tomography of the mediastinum will give false positive scans with regard to lymphadenopathy in about 25% of cases.

A further potential advantage of computed tomography scanning is its ability to identify tumour invasion of the surrounding pleura and chest wall in addition to the mediastinum itself. Goldstraw *et al*[23] found computed tomography more sensitive for identifying mediastinal invasion than for mediastinal adenopathy (77% versus 57%) and also more sensitive than mediastinoscopy (77% versus 46%), especially for lower lobe tumours (67% versus 17%). Not all of the tumours proved unresectable, however. In 18 cases where computed tomography predicted invasion, mediastinoscopy confirmed mediastinal disease contraindicating thoracotomy in 10. The remaining eight patients had resectable tumours. They were all pTNM N0 and had a potentially curative operation. In two cases localised and superficial invasion of the mediastinum was not considered a contraindication to resection.

The available data for computed tomography scanning followed by biopsy or thoracotomy allow certain helpful conclusions to be drawn. (1) The predictive value of a negative computed tomography

scan is of the order of 90–95% and in such cases mediastinoscopy may be omitted before thoracotomy. (2) Similarly, when computed tomography shows the mediastinum to be normal but suggests that the hilum is abnormal mediastinal exploration may also be omitted before thoracotomy. (3) The predictive value of a positive scan is much more variable (50–100%) and therefore mediastinal exploration should be undertaken. In these cases the surgeon should attempt particularly to investigate the abnormality seen on the scan. If mediastinoscopy shows nothing abnormal thoracotomy should be undertaken.

Microscopic mediastinal invasion will be missed by computed tomography and is often not detected at mediastinal exploration. Such invasion may also be missed at thoracotomy unless routine sampling of node stations is undertaken. It is possible that these patients do benefit from surgery.[16] The main advantage of computed tomography is that it can save unnecessary mediastinoscopies. Since, however, it tends to "overstage" tumours, thoracic surgical units without computed tomography scanners will achieve equally good results with routine preoperative mediastinal exploration.

Another non-invasive staging technique—although rarely used in Britain—is scanning with the tumour seeking isotope gallium-67. Gallium-67 is not a tumour specific isotope and will be taken up wherever there is an inflammatory process in the thorax—for example, lymphadenopathy due to tuberculosis, sarcoidosis, or an abscess—but abnormal accumulation of the isotope will occur in 85–90% of all primary lung cancers. Within the thorax the results with gallium-67 are broadly similar to those obtained with computed tomography. Gallium scanning is more sensitive than plain radiography.[25] Its sensitivity for mediastinal metastatic deposits in lymph nodes is about 80%,[25–27] although only those cases where the primary tumour takes up gallium can be realistically assessed. Specificity is also in the region of 80%. While it has been suggested that a positive gallium scan has a sufficiently high predictive accuracy to make mediastinoscopy unnecessary, this view must be criticised as the scans fail to show the anatomical detail seen with computed tomography and would not distinguish nodal disease from mediastinal invasion. This is an important distinction in a few patients and mediastinoscopy would be a helpful procedure. The conclusions of most studies of gallium scanning agree with those of computed tomography reports in suggesting that positive findings in the mediastinum are an indication for mediastinoscopy,[26] while peripheral tumours that take up gallium-67 and have a negative mediastinal scan can be dealt with by thoracotomy without prior mediastinoscopy.[27] On the other hand, the predictive value of negative gallium scans appears too variable to advise forgoing mediastinoscopy for central primary tumours. Recently a comparison of scanning with gallium and bleomycin labelled with cobalt-57[28] showed a greater frequency of uptake by a primary tumour with Co-bleomycin 57 than with gallium (92% versus 54%) and a similar advantage in detecting mediastinal disease (89% versus 45%). Co-bleomycin 57 has, however, the considerable disadvantage of a half life of 270 days.

Surgical staging

In those patients who come to thoracotomy it is important that the staging process is continued. The surgeon's first task is to check the accuracy of preoperative staging, particularly for the unexpected presence and extent of mediastinal gland metastases. If systematic preoperative mediastinal staging has been undertaken the number of irresectable tumours should not exceed 5%,[13] but there may occasionally be cases where the surgeon's preoperative assessment has been so misleading that even at this late stage it is better not to proceed with resection. Mediastinal glands should be sampled from around the pulmonary hilum, routinely including the main carinal glands and one other adjacent gland station. Ideally these glands should undergo frozen section analysis but this is difficult logistically and most surgeons rely on macroscopic appearances. The use of long ambiguous terms to describe gland positions is best avoided. An arbitrary gland numbering system such as those proposed by the American Joint Committee on Cancer Staging and by the American Thoracic Society[17] works well in practice. If resection is subsequently undertaken all glands left on the specimen should therefore be N1 disease.

Despite careful preoperative staging the surgeon may discover macroscopic N2 disease either where the mediastinal exploration has been inaccurate or where glands beyond the reach of the mediastinoscope are discovered. The former case becomes rare with experience but should give rise to careful reconsideration of resectability. In the latter case resection is probably still justified.[16] A further 10% of resections will be found to be N2 only on microscopic analysis of resected nodes.[23]

Pathological staging

It is possible to restage patients as information becomes available from follow up. For practical purposes, however, the most accurate assessment is reached after microscopic analysis of the resected specimens, when a postsurgical treatment-pathological staging (pTNM) can be made. To be meaningful this requires careful presurgical staging

to look for distant metastases, routine sampling of mediastinal gland stations at thoracotomy, and microscopic examination by a pathologist aware of the features of a tumour that affect its stage. The pathologist cannot be expected to differentiate hilar from mediastinal glands included in a resection specimen—this can be difficult enough for the surgeon at thoracotomy. The mediastinal glands should be sent separately and numbered clearly (see above). The pathology report should include comments on the cell type and its differentiation, homogeneity of cell type, pleural disease in the case of peripheral tumours, resection margins and bronchial stump, and the extent of glandular extension and whether such extension is intracapsular or locally invasive.

Staging in small cell lung cancer

The particularly high incidence of mediastinal lymph node disease in small cell lung cancer and coexisting evidence of extrathoracic dissemination at presentation mean that the TNM classification has no bearing on prognosis. Recent surgical series have confirmed the very small number of patients with small cell lung cancers who have truly stage I disease,[29] and large surgical series have included no long term survivors after resection.[1 30] In the few cases where the primary tumour is peripheral, however, survival rates are more favourable, particularly if no nodes are affected; for example, a 60% five year survival rate has been reported in 26 patients with T1 N0 disease.[31] Recently further attempts to improve survival have been made by "debulking" surgery for patients with T1 N0 or T2 N0 lesions followed by combination cytotoxic chemotherapy.[32] Although the great majority of cases of small cell tumours are either clearly inoperable at diagnosis or after extensive staging, there will remain a few patients who should have surgery. Preoperative staging should then be especially thorough and include a computed tomography scan of thorax, abdomen, and brain and bilateral iliac crest marrow aspirations. The role of mediastinoscopy in patients with peripheral small cell tumours with a normal mediastinum on the computed tomography scan is uncertain; but in view of the tendency to disseminate mediastinoscopy would appear to be a sensible final staging procedure. For most patients with small cell tumours staging is somewhat academic. For the purposes of clinical trials and to facilitate comparison of results, staging has been divided simply into limited disease (confined to one hemithorax and ipsilateral supraclavicular fossa) and extensive disease (any disease outside this area). Patients with limited disease comprise about one third of all cases and this number falls with any intensification of staging processes. Patients with limited disease, however, have a longer median survival than those with extensive disease both without treatment (four versus two months) and with chemotherapy (18 versus nine months).

Conclusions

The failure to improve survival in lung cancer is due, firstly, to the very high incidence of obvious inoperability at presentation and, secondly, the lack of sufficiently sensitive tests to identify small metastases in patients otherwise thought curable. Accurate mediastinal staging can make a major contribution to the decision whether to operate. Routine mediastinoscopy will lower the frequency of unnecessary thoracotomies and increase the resectability rate. In the great majority of cases positive findings at mediastinoscopy are associated with incurable disease. In a select group of patients, however—those with squamous cell tumours of the right lung with ipsilateral low superior mediastinal node disease—surgery may still be appropriate. If the findings at preoperative mediastinoscopy are negative and affected glands are found low in the mediastinum at thoracotomy, resection may be beneficial, with a five year survival rate reportedly as high as 41%.[16] Thus thoracotomy resulting from the lack of sensitivity of mediastinoscopy (71%[23]) is not entirely unjustifiable, while the 100% specificity of a positive result[23] ensures that no one is denied surgery inappropriately.

Computed tomography can reduce the number of mediastinoscopies but its specificity is not sufficiently high to eliminate the need for mediastinoscopy in patients with positive scans. Positive findings on computed tomography may also assist by directing the surgeon where to take biopsy samples during mediastinoscopy.

The role of computed tomography in extrathoracic staging is not yet established, but conventional isotope scans are of use only in patients with organ specific or non-specific features suggestive of occult disease.

STEPHEN G SPIRO
PETER GOLDSTRAW
University College and Brompton Hospitals London

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