Preoperative screening for metastases in lung cancer

The objective of thoracotomy and resection for lung cancer is cure of the disease. Cure is difficult to define, but with UK regional survival rates (based on more than 200 resections per annum) of 60–65% at one year, 45–55% at two years, and 38% at five years, it is clear that for many patients surgery does not achieve its aim.1–2 There are many reasons for this—for example, preoperative and immediate postoperative problems, intercurrent illnesses, and later disease recurrence. It is, of course, particularly distressing when unexpected metastatic disease develops after an apparently successful operation.

Precise figures for such metastases are not known. However, evidence from necropsy data3–4 and analyses of the causes of death within a year of surgery suggest that as many as 25–30% of patients may be affected. Thus, with 3200 resections for primary lung cancer currently being performed in the UK each year (United Kingdom Thoracic Surgical Register, 1991) perhaps as many as 1000 patients per annum may have non-curative operations because of unsuspected metastatic disease present at time of surgery.

Preoperative evidence of distant metastases is nearly always an absolute contraindication to surgery. In the early years of thoracic surgery a physician's ability to detect them rested on the combination of history, examination, plain radiographs, tomograms, and blood tests, together with an occasional needle biopsy. With the revolution in medical imaging in the past 10–15 years we now have much more sensitive techniques both for detecting extrathoracic disease, or confirming or denying the clinical suspicion of it. The question now arises whether these scans are being used appropriately or—to pose the problem in another way—how should they be used in an individual case to ensure, within the limits of technology, that patients with metastatic disease do not undergo surgery?

The factors which affect the probability of a potentially operable patient having occult metastases are the intra-thoracic tumour TNM stage and the histology. The one year mortality of patients with non-small cell lung cancer who undergo resection is about 20% for stage I, 35% for stage II, 55% for stage IIIa, and 70% for stage IIIb.5 This increasing mortality with stage is reflected in data on the frequency of metastases. For example, the US Lung Cancer Study group has shown a 12 fold increase in the probability of cerebral metastases comparing T1N2 and T2N2 tumours.6

Stage for stage, the chances of metastases are less for squamous than for adenocarcinoma or large cell anaplastic carcinoma. The US Lung Cancer Study group found that, of 390 resected patients with stage I carcinoma, extrathoracic metastases occurred in 15% of 171 cases of squamous carcinoma and 27% of 209 non-squamous cases.7 Similarly, in 146 patients with non-small cell lung carcinoma staged by thoracic computed tomography (CT), Salvarrieta et al found no metastases in 23 cases of stage I squamous carcinoma, compared with six of 15 patients with stage I adenocarcinoma and large cell carcinoma.8 For stage II the comparison was four of 18 v two of four, and for stage III 16 of 48 v 16 of 37.9 Kormas et al performed preoperative brain CT scans in 158 patients with non-small cell lung carcinoma judged operable after staging which included thoracic CT scanning with mediastinal sampling, upper abdominal ultrasonography, and bone scans.9 Cerebral metastases detected by scanning (five cases) and follow up to one year (five cases) occurred in two of 107 (1.9%) cases of squamous carcinomas compared with eight of 51 (15.7%) patients with non-squamous histology. No metastases were detected by scanning in the 134 patients surgically staged N0 or N1 (stage I), whereas scans were positive in three of 22 patients surgically staged N2 (stage IIIA). Thus, a scanning policy needs to take account both of the preoperative staging and the histological findings.

The sites to be considered for scanning, in addition to the lungs and mediastinum, are the brain, axial skeleton, and upper abdomen. The detection of unexpected ipsilateral or contralateral lung metastases is a further advantage of the routine use of preoperative thoracic CT scanning. Although these scans are only performed in about 60% of cardiothoracic units in the UK at present,10 there is compelling evidence that this, with associated mediastinal lymph node sampling as recommended by the IASLC,11 would reduce the number of ineffective thoracotomies.12 Furthermore, thoracic CT scanning can easily be extended to include the upper abdomen for the detection of adrenal and hepatic metastases.

Isotopic brain scans are too insensitive for routine use. Brain CT is equivalent to magnetic resonance imaging (MRI) for metastases greater than 1 cm in diameter, although it is less sensitive below this size13 and is presently the method of choice because of its wider availability. Isotopic bone scans have a high sensitivity, particularly for non-vertebral metastases,14 but they have a high false positive rate—that is, their specificity for metastases is low. This means that in some cases these scans have to be followed by other tests such as tomograms, CT, MRI, and/or biopsies.15 There is strong evidence from the meticulous study by Michel et al16 that true bony metastases are very rare in patients with lung cancer who are being considered for thoracotomy if there are no symptoms or physical signs whatever, and results of bone biochemistry tests are normal. The only caveat here is that another study17 did show a low false negative rate in patients with N2 disease.

Adrenal and hepatic metastases are usually clinically and biochemically silent. Isotopic liver scans are insensitive, and inferior to abdominal ultrasonography, CT, or
These three techniques are all 100% sensitive for hepatic lesions greater than 2 cm in diameter, whereas CT scanning is somewhat better than both ultrasonography and MRI for smaller lesions. However, scanning alone cannot always distinguish between benign adrenal adenomas and metastases; the former are the cause of about two thirds of adrenal masses in some series, and are relatively common in the normal population. This means that a positive scan may require a subsequent percutaneous needle biopsy for histological confirmation and that a proportion of these will be truly negative.

The specificity, as well as the sensitivity, of scanning techniques has to be borne in mind, therefore, together with the fact that complex confirmatory tests may be needed subsequently.

It becomes apparent that information for making an accurate decision about preoperative scanning ideally would comprise the results from a very large prospective study in non-small cell lung cancer with routine preoperative thoracic CT scans. In patients then thought to be operable there would need to be a record of those patients with any symptoms possibly suggesting metastatic disease according to preset criteria, and for all patients then to have a subsequent brain CT scan, bone scan, and upper abdominal ultrasonographic or CT scan before proceeding to mediastinal sampling and surgery. These scans would need to be followed by comprehensive investigation of indeterminate results, and the whole series should be followed up for at least two years. It is likely that such a study would need more than 1000 patients because of the need to divide the population by cell type and stage.

Unfortunately, despite several decades of publications on this topic, we do not have the results from such a study or studies and thus have to rely on other evidence to form judgements. In this issue of Thorax (pp 14–19) Hillers et al report the results of a literature review which has used assessments of research quality to grade studies, a method which their group has applied elsewhere in the respiratory field.

It is salutary to note that, of the more than 100 reviewed papers, only 17 were judged suitable for detailed analysis. The data on scanning in patients who underwent thoracic CT scanning is confined to five papers only, and the confidence intervals for the chances of detecting metastases in asymptomatic patients remain very wide. Furthermore, there is an understandable problem about the definition of the “asymptomatic” patient, and the paper does not consider the factors of stage and histology as discussed above.

Nevertheless, the resulting figures for the frequency of metastases are worthy of note: 3.3% of 785 patients having brain CT scans had cerebral metastases; 4.7% of 632 had adrenal metastases detected on abdominal CT scanning; 9.3% of 480 had metastases detected by isotopic bone scans; and 2.3% of 529 patients had positive liver ultrasonographic, isotopic, or CT scans. The 95% confidence intervals varied between 2% and 6% around these figures. The number of scans reported in asymptomatic patients with a previous thoracic CT scan as part of their initial examination is far smaller: two of 29 for the brain, none for the adrenal glands, five of 101 for bone, and four of 102 for the liver. These numbers are not large enough for the reader to draw a firm conclusion.

Whether the 3–5% probability of detecting occult metastases in an individual scan justifies a policy of routine scanning and, in particular, whether this is cost effective is a matter for further debate.

In the meantime individual physicians will have to draw their own conclusions from the data. My interpretation would be, firstly, that patients considered for resection should routinely have a thoracic CT scan with contrast medium and an upper abdominal examination at the same time. Asymptomatic patients with stage I squamous carcinoma probably do not justify further scans. Other patients with stage II or stage III disease, even if asymptomatic, probably should have a brain CT scan, and an isotopic bone scan should be performed if there is any suspicion of bone disease after a careful clinical and biochemical assessment. Routine bone scanning in asymptomatic patients is not worthwhile.

The study by Hillers et al neatly summarises our present state of knowledge, and is a suitable starting point for a prospective multicentre study to update the information reviewed in their paper. The collaborative groups working on lung cancer both in the UK, Europe, and in the United States are in a good position to consider providing the additional data we now need.

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