Pathological assessment of mediastinal lymph nodes in lung cancer: implications for non-invasive mediastinal staging


Abstract

Background The use of computed tomography in mediastinal staging of lung cancer relies on the premise that malignant lymph nodes are larger than benign ones. This hypothesis was tested by linking node size and presence or absence of malignancy and looking at factors possibly influencing the size of benign nodes.

Methods All accessible mediastinal lymph nodes were taken from 56 consecutive patients with lung cancer who underwent thoracotomy. Nodes were measured and histologically examined. Resected cancer bearing lung from 44 of these patients was assessed for degree of acute and chronic inflammation.

Results Lymph node size was not significantly related to the presence of metastatic disease, 58% of malignant and 43% of benign lymph nodes measuring over 15 mm. Similarly, there was no statistically significant relation between size of lymph nodes and the likelihood of malignancy, 20% of lymph nodes of 10 mm or more but also 15% of those less than 10 mm being malignant. Thresholds of 15 and 20 mm showed similar results. The maximum size of benign lymph nodes was significantly greater in those patients with histological evidence of acute pulmonary inflammation than in those without.

Conclusions The study shows that in patients with lung cancer (1) malignant mediastinal lymph nodes are not larger than benign nodes; (2) small mediastinal lymph nodes are not infrequently malignant; and (3) benign adenopathy is more common in patients with acute pulmonary inflammation.

Those patients with lung cancer who have mediastinal lymph node metastases have a poorer prognosis than those without. The extent of mediastinal lymph node invasion by tumour may also be important, as Pearson has shown that patients with mediastinal tumour not detected at mediastinoscopy had a better prognosis than those with mediastinoscopy positive disease when both groups were treated by surgical resection. Preoperative mediastinal assessment is therefore important in the selection of patients for thoracotomy. This may be carried out by mediastinoscopy with or without preceding non-invasive techniques, of which the best currently available is computed tomography. Glazer et al, who used computed tomograms of the mediastinum to assess the short axis diameter of the mediastinal lymph nodes, have suggested that those nodes below 15 mm in diameter will be benign and most of those of 15 mm or more will be malignant. Several groups have suggested that this is a very sensitive and specific technique for determining mediastinal lymph node invasion by tumour but other workers have had less encouraging results. A recent meta-analysis of published series suggested that computed tomography will produce a sensitivity of only about 70%, which leaves a considerable margin for error when clinical decisions are being made on individual patients. Computed tomography data are based on analysis of the size of the lymph node, and depend on the belief that malignant lymph nodes will be larger than benign ones and that smaller lymph nodes are more likely to be benign. If this tenet is untrue it could explain the lack of accuracy of computed tomography. We have therefore assessed prospectively the size of lymph nodes removed at thoracotomy from patients with lung cancer and related this to the malignant or benign nature of the nodes. We also set out to establish whether reactive lymphoid hyperplasia could account for lymphadenopathy in patients with pneumonia distal to their tumours by comparing these cases with cases of lung cancer lacking such inflammatory changes.

Patients and methods

Sixty patients who had been accepted for mediastinoscopy or thoracotomy or both were prospectively entered into the study, which has been described elsewhere. Local practice indicated that all patients referred for surgery had a normal mediastinal outline on plain chest radiographs. Six of these patients had media-
Node stations: sampling and rate of malignancy

<table>
<thead>
<tr>
<th>ATS node station</th>
<th>No of occasions sampled</th>
<th>No of node bearing samples</th>
<th>Samples with malignant nodes</th>
<th>Rate of metastatic disease (%)</th>
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stinoscopy, four of whom had malignancy diagnosed at mediastinoscopy and did not proceed to thoracotomy. Fifty six patients underwent thoracotomy; in 44 the lung cancer was considered operable at thoracotomy and lobectomy or pneumonectomy was performed. At thoracotomy all accessible palpable or visible lymph nodes were removed in their entirety, fixed separately in 10% neutral buffered formalin, and labelled according to the American Thoracic Society node station criteria. According to the discussion given in that paper, stations 4 and 10 were considered as mediastinal (N2) in this study. Lung specimens were inflated with 10% neutral buffered formalin and left to fix for at least 24 hours.

After fixation the lymph nodes were individually measured (maximum diameter) and processed in their entirety for histological examination of 5 μm paraffin sections stained with haematoxylin and eosin. At microscopy each node was examined for the presence of metastatic carcinoma. The amount of tumour was estimated by using a point counting technique. In benign lymph nodes note was made of the predominant reactive pattern, if any, present in the parenchyma.

The inflated lung specimens were cut in parallel 1 cm thick parasagittal slices. In addition to routine examination of the tumour, we recorded evidence of distal obstructive pneumonitis (endogenous lipid pneumonia, purulent bronchiectasis, pneumonic consolidation, and abscess formation) and noted its extent on the basis of segmental anatomy. Tissue from the tumour and the lung parenchyma was sampled for histological examination and the lung parenchyma examined for evidence of lymphoid infiltrates, organising or endogenous lipid pneumonia, interstitial fibrosis, and pyogenic inflammation.

Acute inflammation was recorded as either "nil" or "positive." The microscopic appearances of tissues sampled from abnormal areas reflected the macroscopic appearances. Microscopic evidence of appreciable acute inflammation was not seen in the absence of gross evidence of pus. Accumulation of a few bronchial or alveolar neutrophil polymorphs was ignored.

Chronic inflammation was graded as "nil," "minimal," or "positive." Changes could be identified microscopically when there was little to be seen macroscopically, though in such cases the histological features were less abundant. These cases were graded as "minimal."

The "positive" cases were those with evidence of macroscopic change and commensurate histological features.

Results

Of the 56 patients who had a thoracotomy, 30 had squamous carcinoma, 14 adenocarcinoma, three mixed adenosquamous carcinoma, four large cell carcinoma, and five small cell undifferentiated carcinoma.

From the 54 thoracotomies at which mediastinal lymph nodes were obtained 168 lymph nodes were submitted for examination. Thirty one (18%) of these nodes were malignant. Twenty one (37%) of 54 patients had mediastinal metastases. The table shows the number of times tissue was taken from each node station. In total, 111 stations were sampled (mean 2.1 (range 1–7) stations per patient). On eight occasions there were no lymph nodes in the tissue submitted. Node station 2 (high mediastinum, upper and mid peritracheal region) had the highest rate of malignant samples (43%). The rates for stations 7, 8, and 9 (subcarinal, paraoesophageal, and pulmonary ligament) were among the lowest (14%, 12%, and 11%) even though stations 7 and 8 were those most often sampled. The three samples from station 6 (anterior mediastinal) were all benign. Fourteen of the 21 patients with mediastinal metastases had more than one station sampled. Only three of these 21 showed tumour at all stations sampled, 11 cases having both benign and malignant stations (23 benign versus nine malignant stations in total). In five of these 11 patients the malignant station also contained the biggest node recovered from the mediastinum.

Figure 1 shows the size of all the mediastinal lymph nodes recovered from thoracotomy plotted with maximum node size versus area of nodal cross section, as percentage, found to be replaced by tumour on histological analysis. Benign nodes are grouped on the left.
lymph nodes plotted against the proportion of node replaced by tumour. There is no tendency for malignant lymph nodes to be larger than benign nodes. Malignant lymph nodes where the node is replaced by tumour are not necessarily larger than nodes containing microscopic metastases. If we take a cut off point of 15 mm, 58% of all malignant mediastinal nodes but also 43% of benign nodes measured 15 mm or more. Figure 2 illustrates groups of nodes having maximum diameters with a range of threshold values. There is no size, in the range of values chosen, that increases the proportion of nodes that are malignant. Equally noteworthy, a substantial proportion of “small” lymph nodes are also malignant. To allow comparison with the data in figure 2, malignancy rates for all nodes less than 10, 15, and 20 mm in diameter are 15%, 14%, and 17%. For each threshold size \( \chi^2 \) analysis indicates that the larger nodes are no more likely to be malignant than the smaller ones (0.5 > \( p > 0.1 \) in each instance).

There is no tendency for the largest malignant mediastinal lymph nodes to be larger than their benign counterparts (fig 3). Similarly, there is no significant relation between the size of the largest node obtained from each patient’s mediastinum, irrespective of whether benign or malignant, and the overall benign or malignant nature of the mediastinal lymph nodes in that patient (fig 4).

Of the 44 patients who had thoracotomy and lung resection, allowing lung inflammation to be assessed, 42 had mediastinal nodes submitted for examination. One patient was incidentally found to have sarcoidosis and was thus removed from this part of the study. He had microscopic metastatic disease but massive granulomatous lymphadenopathy. In the two cases where resection was performed but mediastinal nodes could not be found by the surgeon, each lung specimen was scored “nil” for both acute and chronic inflammation. Of the remaining 41 cases with nodes submitted, there were 15, nine, and 17 cases respectively with

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**Figure 2** Medialstinal lymph node groupings defined by lower limits of size range showing the proportion of each grouping that is malignant.

<table>
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<tr>
<th>Maximum diameter (mm)</th>
<th>n:</th>
<th>% of total malignant</th>
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<tbody>
<tr>
<td>=5</td>
<td>158</td>
<td>19%</td>
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<tr>
<td>=10</td>
<td>120</td>
<td>20%</td>
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<tr>
<td>=15</td>
<td>77</td>
<td>23%</td>
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<tr>
<td>=20</td>
<td>43</td>
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**Figure 3** Size of largest benign and, when present, malignant lymph node in the mediastinum of the patients under study. Some patients had only one type of node. Some had both and thus their largest benign and malignant nodes were included in these data. The bar indicates the arithmetic mean. NS—no significant difference. \( p = 0.57 \), Student’s \( t \) test.

**Figure 4** Size of the largest mediastinal lymph node, whether benign or malignant, recovered from each patient plotted against the histologically proved status—benign or malignant—of that patient’s mediastinum. Bars indicate the arithmetic mean. NS—no significant difference. \( p = 0.83 \), Student’s \( t \) test.
individual, the ones most likely to cause concern to clinician and radiologist, and the presence of metastatic lymphadenopathy. Pathologically defined acute pulmonary inflammation was associated with appreciable benign lymphadenopathy.

The finding of the lack of relationship between lymph node size and probability of malignancy helps to clarify the limitations of the use of computed tomography in the staging of the mediastinum in lung cancer. Current imaging techniques can determine only the size and not the histological nature of lymph nodes.

All palpable or visible lymph nodes were removed at thoracotomy, though a full mediastinal clearance was not carried out. Although this, potentially, biases our results appreciable lymphadenopathy or “large” nodes are unlikely to have been missed. Many of our data relate to the largest nodes present. An increased yield of “small” nodes of, perhaps, less than 5 mm would have little effect on our numerical data or conclusions apart from depressing even further the overall rate of malignancy. In the light of our finding of considerable numbers of “small” lymph nodes containing malignancy, however, small lymph nodes potentially “missed” by the surgeon would clearly be of interest.

Our data are derived from a small and selected group of patients. None the less, it is in such patients that knowledge of the malignant or benign nature of the nodes is important and may influence decisions about management. Although not complete (see above), our harvesting of nodes is more extensive than in many other studies. Our procedure for selecting patients meant that those whose clinically gross mediastinal lymphadenopathy did not come to thoracotomy. We have compared actual node size with the malignant or benign nature of the node. This is quite a different matter from relating measurements of computed tomographic node size to the presence or absence of metastatic disease as reported by a pathologist. Libshitz and McKenna did make actual measurements of lymph nodes as well as computed tomographic measurements. Their conclusions regarding preoperative computed tomographic staging are guarded—rather like ours.

As mentioned above, the measurements made in this study were of maximum node dimension made on pathological specimens. These are not directly comparable to measurements taken from computed tomographic images, which are usually the short axis diameter of lymph nodes in the horizontal plane, because lymph nodes are rarely spherical. None the less, trends of size within groups of nodes will still be representative. Thus, although the threshold dimensions given in figure 2 and elsewhere were chosen to compare with sizes used in computed tomographic studies, direct comparison is not intended. They serve to emphasise, however, that varying the threshold within the clinically relevant range neither significantly increases the rate of malignancy in “large” nodes nor reduces it for “small” nodes.

**Discussion**

This study shows that in patients with potentially operable lung cancer there is no clear relation between the size of a mediastinal lymph node and the probability of malignancy therein. There is also no relation between the size of the largest lymph node or nodes in an

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*Figure 5* Largest benign mediastinal lymph node size plotted against the combined acute inflammation score derived from resected lung. Bars indicate the arithmetic mean. $p = 0.01$, Student's $t$-test.

Chronic inflammation graded as “nil,” “minimal,” and “positive.” The mean maximum sizes of benign mediastinal nodes were 18 (SE 2), 17 (2), and 22 (2.5) mm respectively for the groups, with no significant difference between them. The 41 cases divided very clearly on being classified for acute pulmonary inflammation into negative and positive groups (28 and 13 cases). The mean maximum diameter of the largest benign mediastinal lymph node in the group with acute lung inflammation was 24 (SE 2) mm, and this was significantly higher than the value for those cases without acute inflammation (17 (1.5) mm; $p = 0.01$, Student's $t$-test; fig 5). The degree of node enlargement seen in benign lymphadenopathy equals or exceeds that seen in metastatic nodal disease.

In the 13 cases with a “positive” acute pulmonary inflammation score the reactive lymph nodes showed a predominance of follicular hyperplasia, accounting for increase in node size in nine (70%) cases. Such follicular hyperplasia was present in only two out of 28 (7%) cases devoid of appreciable acute inflammation.
This study confirms the views of others that computed tomography can be used to guide lymph node sampling before resection only when enlarged nodes are detected on the scan.7 11 15 The finding of considerable numbers of malignant nodes in the "small" lymph node category, regardless of how that group is defined (whether in terms of 10 or 15 mm thresholds), also calls into question the confidence placed in a "negative" mediastinal scan.16 This, inevitably, leads us to question whether all such patients should have mediastinoscopy before thoracotomy. It may be of interest, with this in mind, that node station 2 had the highest malignancy rate in our study.

With or without this practice some patients with "negative" computed tomograms will have later thoracotomy have mediastinal node positive disease.15 Possibly, however, some patients with N1 disease benefit from surgery.1

Even if computed tomography detects enlarged nodes, benign or malignant, in the mediastinum of a patient with lung cancer, is there an association between enlarged mediastinal lymph nodes and mediastinal malignancy, not necessarily within the enlarged nodes? Figure 4 illustrates that there is no such relation. Malignant mediastinums do not have larger lymph nodes than benign mediastinums.

Factors other than metastatic malignancy that might account for benign mediastinal lymph node enlargement are clearly important. A small percentage of cases will have sarcoidosis, sarcoid reactions, granulomatous lymphadenopathy, or anthrakosilosis, depending on the local population. More common is non-specific reactive hyperplasia, which can account for a very substantial increase in lymph node size, including the largest nodes removed in this study. Possible reasons for the lymphoid hyperplasia include pulmonary inflammation related to the tumour—that is, obstructive pneumonitis, distal infection, and immunological reaction to tumour antigens. There is some data relating radiological evidence of obstructive pneumonitis with apparent lymph node enlargement and an awareness that caution must be shown in interpreting enlarged mediastinal nodes in these circumstances.14 18 On the other hand, others have shown no relation between radiologically diagnosed pneumonitis and node size.19 Our study shows a significant increase in lymph node size with acute but not chronic inflammation. Except for abscess formation, which may be radiologically detectable, the chronicity of inflammatory consolidation cannot be determined by imaging. Other clinical variables of infection associated with acute pyogenic inflammation may, of course, be present. It is doubtful, however, whether this would be useful clinically as the overlap of results in the two groups in figure 5 is still substantial. The association of follicular hyperplasia with lymphadenopathy seen in acute obstructive pneumonitis is not unexpected. Most of these cases of pneumonia will be bacterial, eliciting a B cell humoral response within the draining lymphoid tissue.

This study shows that malignant lymph nodes in the mediastinum in this group of patients with lung cancer are no larger than their benign counterparts. Most nodes considered enlarged in these circumstances are benign and many small lymph nodes still contain metastatic disease. It would seem that the central tenet questioned at the beginning of this paper is not sound. This implies that increasing the sensitivity and resolution of computed tomography scanners will not improve their ability to detect lymph node metastases. The presence of metastatic disease in 15% of relatively small lymph nodes calls into question the confidence that might be put in a so-called "negative" mediastinal computed tomogram.

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14 Lishibiz H1, McKenna RJ. Mediastinal lymph node size in lung cancer. AJR 1984;143:715-8.