

Original articles

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

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Abstract

Background The use of computed tomography in mediastinal staging of lung cancer relies on the premiss 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.¹⁻³ 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.⁴ Preoperative mediastinal assessment is therefore important in the selection of patients for thoracotomy. This may be carried out by mediastinoscopy⁵ 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.⁶ Several groups have suggested that this is a very sensitive and specific technique for determining mediastinal lymph node invasion by tumour^{7,8} but other workers have had less encouraging results.⁹ 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.¹⁰ 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.¹¹ Local practice indicated that all patients referred for surgery had a normal mediastinal outline on plain chest radiographs. Six of these patients had media-

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Node stations: sampling and rate of malignancy

ATS node station ¹²	No of occasions sampled	No of node bearing samples	Samples with malignant nodes	Rate of metastatic disease (%)
2	17	14	6	43
4	12	10	2	20
5	14	13	4	31
6	3	3	—	—
7	21	20	3	14
8	18	17	2	12
9	9	9	1	11
10	17	17	4	24

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.¹² 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.¹³ 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 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

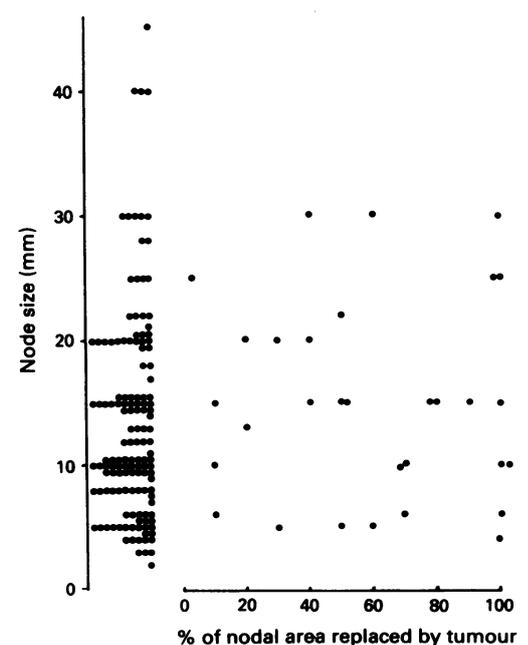
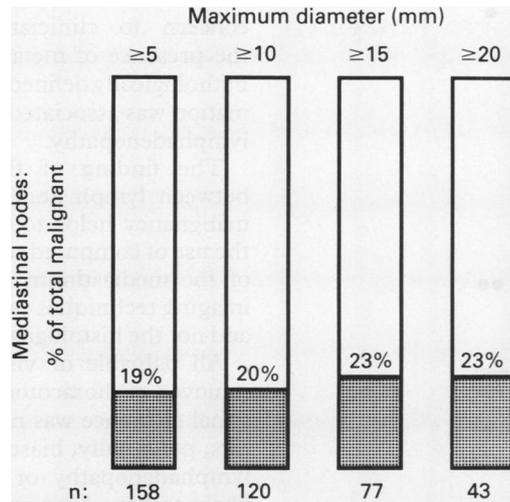


Figure 1 All 168 mediastinal lymph nodes recovered from thoracotomy plotted with maximum node size versus area of nodal cross section, as percentage, found to be replaced by tumour on histological analysis. Benign nodes are grouped on the left.

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



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 χ^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

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.

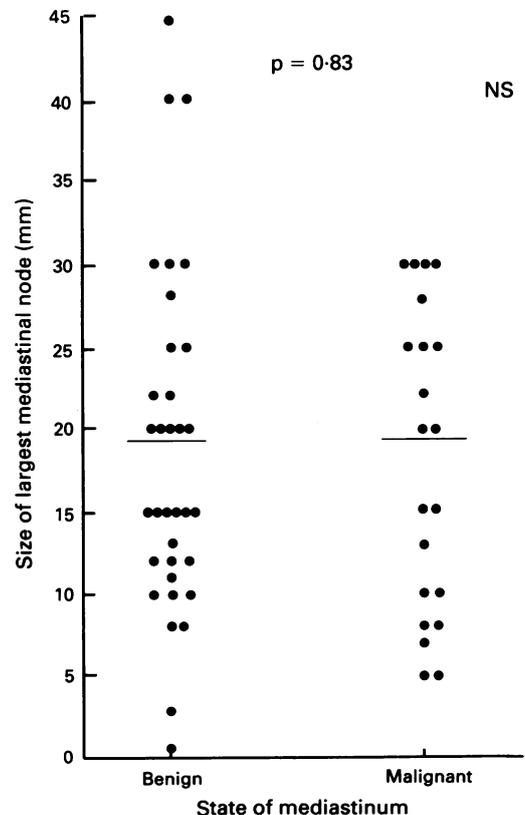
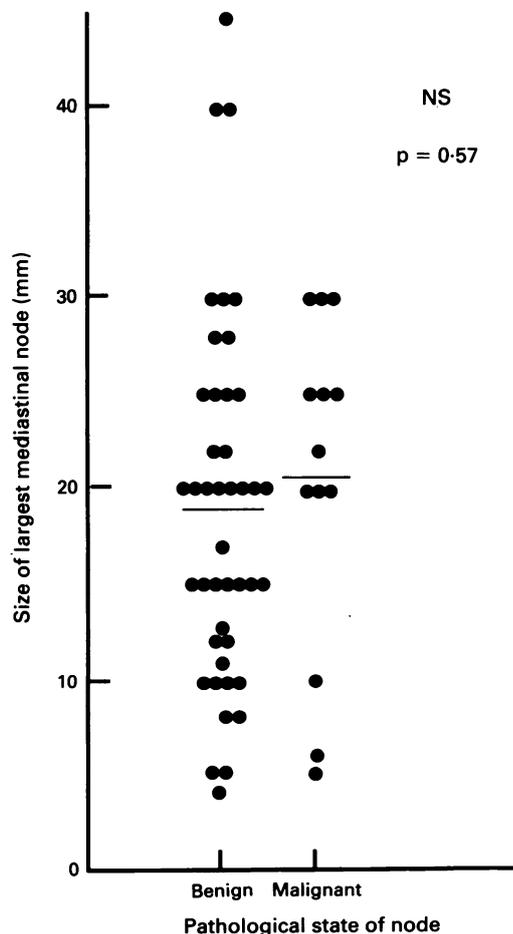


Figure 4 Size of the largest mediastinal lymph node, whether benign or malignant, recovered from each patient plotted against the histologically proved status—benign or malignant—of that patient’s mediastinum. Bars indicate the arithmetic mean. NS—no significant difference. $p = 0.83$, Student’s *t* test.

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 after thoracotomy have mediastinal node positive disease.¹⁵ Possibly, however, some patients with N₂ 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 anthrosilicosis, 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 are 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.¹⁵ 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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