A Comparison of Cobalt (57Co) Bleomycin Scanning and Contrast-Enhanced CT Scanning for Assessment of the Mediastinum in Lung Cancer*

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Sixty patients with histologically proven lung cancer who had been accepted for mediastinoscopy or thoracotomy were prospectively entered into a study to evaluate computed tomographic (CT) scanning, 57Co-bleomycin scanning, and barium swallow in preoperative assessment of mediastinal lymph node metastasis. Fifty-six patients had thoracotomy at which all accessible lymph nodes were sampled. Twenty-four patients were found to have mediastinal tumor on histologic analysis of the resected mediastinal lymph nodes. Neither 57Co-bleomycin scanning nor barium swallow were clinically useful, with sensitivities of 21 percent and 11 percent respectively, whereas CT scanning was helpful. However, there was no clear cutoff point of node size to optimize sensitivity and specificity for CT scanning. When nodes ≥15 mm were taken to indicate likely malignancy, the sensitivity was 58 percent and the specificity was 87 percent and when ≥10 mm was used the sensitivity was 80 percent but the specificity was only 55 percent. There was no clear relationship between the size of the largest resected lymph node in each patient and the presence of malignant lymph nodes. Only 42 percent of patients with resected nodes ≥2 cm had histologic evidence of metastases. We conclude that CT scanning should be used to indicate the presence and site of mediastinal lymph nodes, which, when visualized, should always be sampled and histologically examined prior to resection of primary tumor. (Chest 1990; 97:1149-51)

It is important to establish the site and extent of mediastinal lymph node metastases in patients with lung cancer. Patients with malignant mediastinal nodes have a poorer prognosis.1-3 In addition, the position of involved lymph nodes may affect survival,4,5 those patients with isolated subcarinal or low mediastinal involvement faring better than those with high mediastinal involvement or involvement in the subcarina and another site.6 There is debate as to whether mediastinal lymph node involvement is a contraindication to resection, some believing this to be the case for adenocarcinoma and small-cell carcinoma,6 but not for squamous cell carcinoma.7

A noninvasive technique that could accurately assess mediastinal lymph node involvement with tumor would therefore be extremely useful. Computed tomographic (CT) scanning is the most widely used noninvasive method of staging the mediastinum, although its role is still being evaluated. Early studies8,9 with 57Co-bleomycin scanning have proved promising with a high detection rate and no false-positive scans.9 However, relatively few patients have been investigated using this technique. In Edinburgh, staging of the mediastinum has traditionally been carried out by barium swallow using deviation of the barium column as a method of detecting enlarged mediastinal lymph nodes, although no formal assessment of this technique has been carried out.

We have therefore compared contrast-enhanced fast breath-hold CT scanning of the mediastinum with 57Co-bleomycin scanning and barium swallow for assessment of the mediastinum in a prospective study of patients with histologically proven lung cancer who had been accepted for surgery.

**Patients and Methods**

Sixty patients with histologically proven lung cancer who had been accepted for surgery were studied. Fifty-six of the 60 patients had open thoracotomy, only four having mediastinoscopy and not proceeding to thoracotomy. There were 48 men and 12 women aged 48 to 78 years (mean ± SD, 63 ± 7 years), all of whom had been referred to the Regional Thoracic Surgical Unit at the City Hospital, Edinburgh. All had a barium swallow, 57Co-bleomycin scan, and fast breath-hold CT scan of the thorax with contrast less than two weeks prior to surgery. The results of these investigations were not known to the surgeon at the time of operation.

**CT Scanning**

Computed tomographic scanning was carried out during breath-hold using a CT scanner (IGE 8800) with a scan time of 3 s. A
dynamic series of scans of 1 cm were taken at intervals of 1 cm to the carina and 1.5 cm below that. Contrast injection (100 ml) was used for enhancement of the vascular structures in every patient except one who was allergic to iodine (she had a normal mediastinal CT scan). In all cases the CT scans were reported jointly by two experienced radiologists using a standardized format to record the lymphadenopathy in short axis size and site by the American Thoracic Society (ATS) classification. The radiologists were blinded to all other information.

\textbf{\textsuperscript{99}Co-Bleomycin Scanning}

The \textsuperscript{99}Co-bleomycin scans were carried out 24 h after the injection of 40 MBq of bleomycin labeled with cobalt 57. The \textsuperscript{99}Co-bleomycin was prepared from cobaltous chloride (\textsuperscript{57}Co) (CIS UK Ltd, High Wycombe, UK) and bleomycin (Lundbeck Pharmaceuticals, Luton, UK) as described by Nieweg et al. In each case the radiochemical purity of the radiopharmaceutical was measured by thin layer chromatography and in all cases the unlabeled \textsuperscript{57}Co was less than 3 percent of the total. The injection for each patient contained 40 MBq of cobalt combined to 2.5 mg of bleomycin. Urine was collected for 24 h and the scanning was carried out using a large field of view, low-energy gamma camera (Siemens) connected to a microcomputer (Link Systems) with software to enhance the images. In each patient anterior and posterior views were taken and all the scans were reported by one experienced operator. The scanning time was up to 30 minutes. The radiologist was blinded to the results of the other investigations.

\textbf{Barium Swallow}

Barium swallows were carried out under screening by one experienced radiologist.

\textbf{Pathologic Assessment}

Four patients had abnormal results at mediastinoscopy and did not proceed to thoracotomy. At operation all accessible lymph nodes were removed and labeled according to the ATS classification. The nodes were separately fixed in formaldehyde solution. One pathologist measured the maximum diameter of each node and processed it in its entirety. The pathologist also examined the resected tumor in the standard fashion after inflation of the lung.

For this study the histologic involvement of lymph nodes by tumor has been regarded as the "gold" standard and the sensitivity and specificity of each of the noninvasive investigations have been calculated. The variation on the relationship between sensitivity and specificity with size of the lymph node detected on the CT scan was assessed by plotting the receiver operating characteristic curve.

\textbf{RESULTS}

Of the 60 patients, 35 had squamous carcinoma, including three with a mixed squamous and adenocarcinoma; 15 had adenocarcinoma, four had large-cell undifferentiated carcinoma, and six had small-cell carcinoma. In 24 cases there was histologic evidence of tumor in mediastinal lymph nodes (N2).

\textbf{CT Scanning}

The receiver operator characteristic curve illustrating the relationship between reported node size on CT scan with sensitivity and specificity (Fig 1) does not indicate a clear break point in node size which gives the best compromise of sensitivity with specificity. Calling scans positive in which lymph nodes greater than 15 mm were detected, there were 14 true-positive scans, five false-positive scans, ten false-negative scans, and 31 true-negative scans (Table 1). If a CT node size of 9 and $\geq$10 mm were considered malignant there were 19 true-positive scans, 15 false-positive scans, six false-negative scans, and 20 true negative scans.

\textbf{\textsuperscript{57}Co-Bleomycin Scanning}

All patients had \textsuperscript{57}Co uptake detected by the gamma camera in the region of the primary lung tumor. However, mediastinal lymph node involvement was poorly detected by \textsuperscript{57}Co scanning with only five true-positive scans and 19 false-negative scans. Hence the sensitivity was 21 percent and the specificity was 94 percent (Table 2).

\textbf{Barium Swallow}

There were only four positive barium swallows but no false-positive results (Table 2).

\textbf{Pathology}

Long axis size of the mediastinal lymph nodes measured after fixation in formaldehyde solution revealed that mediastinal tumor metastases were present in only 42 percent of patients with mediastinal lymph

\begin{table}
\centering
\caption{Sensitivity and Specificity for CT Scans Calculated for Different Sizes of Nodes Considered Malignant}
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Node Size} & \textbf{$\geq$20 mm} & \textbf{15-19 mm} & \textbf{10-14 mm} & \textbf{<10 mm} \\
\hline
\textbf{Sensitivity, \%} & 46 & 58 & 80 & 100 \\
\textbf{Specificity, \%} & 92 & 87 & 55 & 8 \\
\hline
\end{tabular}
\end{table}
nodes ≥2 cm in diameter, 28 percent of patients with largest nodes 15 to 19 mm in diameter, and 29 percent of patients with no nodes <14 mm in diameter (Table 3). Direct comparison of measured lymph node size and CT derived short axis size is not possible but the sites from which the large nodes were removed agreed reasonably well with the sites where CT scan had identified enlarged nodes. All five false-positive CT scans (≥15 mm cut off) identified large nodes in the subcarinal region. Pathologically, four of the patients had benign nodes ≥2 mm in diameter (node sizes 5, 15, 20, 22, and 40 mm) at this site.

**DISCUSSION**

In this study CT scanning was the best procedure for detecting mediastinal lymph node involvement by tumor. However, the technique is imperfect largely because of the considerable number of abnormal scans in which no malignant nodes were found. Because patients were entered into the study prospectively and the information obtained from the CT scan, barium swallow, and 57Co-bleomycin scan was not used to determine management, it was possible to obtain accurate histologic analysis of all accessible lymph nodes in every patient. This is in contrast to previous studies that have often been retrospective and usually have not involved removal of all accessible lymph nodes. In some studies the results of investigations have been used to influence management.

**Table 3—Relationship between Lymph Node (LN) Size and Malignancy**

<table>
<thead>
<tr>
<th>Metastases, No. (%)</th>
<th>Largest pathologic LN size</th>
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<tbody>
<tr>
<td></td>
<td>≥2 cm (n = 26)</td>
</tr>
<tr>
<td></td>
<td>15-19 mm (n = 9)</td>
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<tr>
<td></td>
<td>10-14 mm (n = 10)</td>
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<td></td>
<td>&lt;10 mm (n = 11)</td>
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<tr>
<td>Largest CT LN size</td>
<td>≥2 cm (n = 11)</td>
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<tr>
<td></td>
<td>15-19 mm (n = 7)</td>
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<tr>
<td></td>
<td>10-14 mm (n = 18)</td>
</tr>
<tr>
<td></td>
<td>&lt;10 mm (n = 24)</td>
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</table>

*Comparison of largest lymph node size recorded by pathologic study (above) or CT scan (below) in each patient with the likelihood of histologic evidence of tumor on mediastinal nodes in that patient. For pathologic measurement, n = 56, excluding four patients who had mediastinoscopy only as largest pathologic lymph node size could not be assessed.

and thus patients with positive scans may have been excluded from surgery and analysis. This patient selection may explain the differences between our own study and many reported studies.

Our CT scanning results differ from those in many previous series in showing lower sensitivities at the thresholds previously used to indicate likely malignancy, 10, 15, and 20 mm. This almost certainly results from the fact that all accessible lymph nodes were removed and examined histologically in contrast to previous studies in which only enlarged nodes were sampled at the time of surgery. One study using a 15-mm threshold for positive CT nodes suggested that their sensitivity rate would have fallen from 71 to 63 percent if the prospective policy of examining all lymph nodes had been followed. Our results are compatible with those recently reported in three prospective studies and from a preliminary report of the analysis of 43 studies of mediastinal staging in lung cancer. From our data it can be seen that enlarged mediastinal lymph nodes are often benign, showing reactive change (n = 21, ≥15 mm) or in one case, sarcoidosis (Table 3). The short transverse axis CT measurement of lymph nodes cannot be directly compared with the long axis measurement of the formaldehyde solution-fixed lymph node. However, the pathologic data show that no increase in the quality of CT scanning images is likely to improve the results of this technique as large benign lymph nodes were common. This study thus reinforces the importance of always obtaining a tissue diagnosis from mediastinal nodes.

Our receiver operating characteristic curve differs from that previously reported by Glaser et al in reflecting the lower sensitivity resulting from the prospective sampling of all accessible lymph nodes. There is no clear-cut threshold node size that offers a clear advantage from the compromise between sensitivity and specificity.

Our data show that 57Co-bleomycin scanning has no place in the assessment of the mediastinum in lung cancer. This is in contrast to the earlier report of Nieweg et al, but our series is larger and we have been able to distinguish the mediastinal nodes (N2) from the hilar nodes (N1). Further, the other study contained false positives in patients with pneumonia and other inflammatory conditions where 57Co-bleomycin was taken up in the lung. This is not surprising as bleomycin is taken up into dividing cells. In view of the resolution characteristics of the gamma camera and the long scanning times required, it is perhaps not surprising that the technique is poor for identifying mediastinal lymph nodes. Barium swallow has a very low sensitivity but in contrast to 57Co-bleomycin it did have the advantage that there were no false-positive results so patients would not be excluded from surgery.
on the basis of a misleading positive result.

This study indicates that CT scanning is the best available method of noninvasively assessing mediastinal lymph node involvement with tumor. Our results suggest that any lymph nodes detected on CT scan should be sampled by mediastinoscopy, mediastinotomy, or thoracotomy, depending on accessibility and histologic data obtained prior to resection.

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