Mediastinal Spread of Metastatic Lymph Nodes in Bronchogenic Carcinoma

Mediastinal Nodal Metastases in Lung Cancer

Yoh Watanabe, M.D., F.C.C.P.; Junzo Shimizu, M.D.; Makoto Tsubota, M.D.; and Takashi Iwa, M.D., F.C.C.P.

The location, frequency, and spread of metastases to the mediastinal lymph nodes were examined in 124 patients with histologically proven N2 disease who underwent pulmonary resection and total lymph node resection. There were one-level metastases in 47 percent of cases, two-level metastases in 29 percent, three-level in 12 percent, and 12 percent had four or more levels of metastases. Nodal metastases to the lower mediastinum from upper lobe cancer were frequently observed as were metastases of lower lobe cancer to the upper mediastinum. The frequency of the latter was higher than that of the former. About one third of squamous cell carcinoma and adenocarcinoma in the right upper lobe produced nodal metastases in the lower mediastinum. In addition, there were often skip metastases to the nonregional parts of the mediastinum without regional nodal involvement in the mediastinum. From the results of the present study, it appears that extensive mediastinal dissection should be recommended in surgery for lung cancer irrespective of the location of the primary tumor.

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In lung cancer, the presence of mediastinal lymph node metastases is one of the most important factors determining the prognosis.1-3 The incidence of mediastinal metastases generally becomes higher as tumor size increases. Also, there are many cases in which latent (microscopic) metastases are present, even if the tumor is less than 3 cm in diameter (T1 lesion). Furthermore, there is a relatively high incidence of involvement of mediastinal nodes far removed from the location of the primary tumor. For instance, cancer in the right upper lobe can produce nodal metastases in the lower mediastinum. These facts support the proposition that extensive mediastinal lymph node dissection should be undertaken in surgery for bronchogenic carcinoma, even if the primary tumor is small and no nodal metastases are present on gross examination.

We analyzed the patterns of mediastinal metastasis in bronchogenic carcinoma in relation to tumor size, cell type, and the location of the primary lesion by postoperative histopathologic examination of specimens from patients who underwent complete resection of the primary tumor plus lymph node dissection.

Materials and Methods

Over the past 15 years, 976 patients with lung cancer were admitted to The Department of Surgery of Kanazawa (Japan) University School of Medicine. Of these, 744 underwent thoracotomy and 717 underwent lung resection. As a curative operation for lung cancer, all of the visible lymph nodes in the resected lobe, hilum, and mediastinum on the ipsilateral side were removed in accordance with the lymph node map shown in Figure 1.

In 540 of 717 patients undergoing tumor resection, a definitive pulmonary resection with complete nodal dissection was performed (Table 1). There were 241 cases (45 percent) of squamous cell carcinoma, 212 cases (39 percent) of adenocarcinoma, and 87 cases (16 percent) of other types of cancer. By postoperative microscopic examination of the dissected lymph nodes, it was found that 332 patients (61 percent) had N0 lesions and 84 patients (16 percent) had N1 lesions. One hundred seventy-nine patients were verified as having N2 disease, but 55 of them were excluded from this study for having distant metastases, incomplete resection of the primary tumor, incomplete nodal dissection, metastases in the contralateral hilum or mediastinum (N3 lesion), or limited lung resection without node dissection. As a result, there were 124 remaining patients with N2 lesions in whom definitive pulmonary resection with complete dissection of hilar as well as mediastinal lymph nodes had been performed (Table 1). These 124 cases (23 percent of the 540 cases of radical resection) were selected for the present study. There were 91 male and 33 female patients.

In the operations for cancer of the right lung, all of the lymph nodes in the ipsilateral mediastinum (shown in Fig 1) could be dissected without difficulty. Therefore, all of the patients with right-sided lung cancer underwent operative procedures that were almost the same over the past 15 years. However, for left-sided lesions, the procedure for dissecting mediastinal lymph nodes was slightly modified in recent years. From 1980, to allow better dissection of the lymph nodes located behind the aorta, mobilization of the aortic arch was employed as a standard procedure in left-sided lung cancer. In addition, since 1986, to allow more complete and extensive dissection of the mediastinal lymph nodes, median sternotomy was performed in selected cases after procedures in the left hemithorax had been completed using a posterolateral approach.4 The candidates for this operative procedure were selected from those who clinically had N2 disease on preoperative examination or were found to have N2 disease intraoperatively.

During the operation, all resected lymph nodes were placed into the small compartments of a lymph node box in which each lymph......
node level was separately numbered. All of these lymph nodes were sent for pathologic examination. There were several cases that had multiple metastatic lymph nodes within one level; however, they were calculated as one metastatic focus in this comparison.

For comparison of metastatic spread to the mediastinum, the 124 patients were divided into four groups according to the location of the primary tumor: a group with right upper lobe primaries, a group with right middle or lower lobe primaries, a group with left upper lobe primaries, and a group with left lower lobe primaries. To examine the frequency of skip metastases to the nonregional mediastinum, the mediastinal nodes were separated into two regions, the upper and the lower mediastinum. The upper mediastinum contained nodes 1 through 4 on the right side and nodes 1 through 6 on the left side. The lower mediastinum contained nodes...
Table 1—Frequency of N0, N1, and N2 in Patients Who Underwent Curative Surgery

<table>
<thead>
<tr>
<th>Cell Type*</th>
<th>SQ</th>
<th>AD</th>
<th>A-E</th>
<th>L</th>
<th>S</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1, N0, M0</td>
<td>37</td>
<td>69</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>120</td>
</tr>
<tr>
<td>T2, N0, M0</td>
<td>75</td>
<td>53</td>
<td>136</td>
<td>5</td>
<td>6</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>T3, N0, M0</td>
<td>21</td>
<td>11</td>
<td>16</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>T4, N0, M0</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>T1, N1, M0</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>T2, N1, M0</td>
<td>25</td>
<td>11</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>47</td>
</tr>
<tr>
<td>T3, N1, M0</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>T4, N1, M0</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>T1, N2, M0</td>
<td>2</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>T2, N2, M0</td>
<td>19</td>
<td>30</td>
<td>55</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>57</td>
</tr>
<tr>
<td>T3, N2, M0</td>
<td>28</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>T4, N2, M0</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>241</td>
<td>212</td>
<td>24</td>
<td>20</td>
<td>26</td>
<td>17</td>
<td>540</td>
</tr>
</tbody>
</table>

*SQ = squamous cell carcinoma; AD = adenocarcinoma; A-E = adenosquamous carcinoma; L = large-cell carcinoma; S = small-cell carcinoma; Other = other types of cancer.

7 through 9 on both sides. If the primary lesion was located in the upper lobe, the upper mediastinum and lower mediastinum were respectively designated as the regional and nonregional mediastinum. With lower lobe lesions, the lower mediastinum was designated as the regional mediastinum and the upper mediastinum was designated as the nonregional mediastinum. If a primary tumor was located in the right upper lobe and had mediastinal metastases in the ipsilateral lower mediastinum without nodal metastases to the upper mediastinum, these were designated as skip mediastinal metastases.

Staging of all of the patients was performed using the new TNM classification proposed by the UICC in 1986 following postoperative examination of the resected specimens.

Results

The histologic diagnosis was squamous cell in 53 patients, adenocarcinoma in 55 patients, adenosquamous carcinoma in seven patients, large-cell carcinoma in two patients, small-cell carcinoma in six patients, and other type of cancer in one patient (Table 1). The location of the primary tumor was the right upper lobe in 45 patients, right middle or lower lobe in 36 patients, the left upper lobe in 35 patients, and the left lower lobe in eight patients.

Effect of Histologic Type on the Extent of Mediastinal Nodal Metastasis

In Table 2, the extent of mediastinal lymph node metastasis is shown in relation to each histologic type. In 53 patients with squamous cell carcinoma, 58 percent (31/53) had one-level metastases, 21 percent (11/53) had two-level metastases, and 11 percent (6/53) had three-level metastases. Nine percent (5/53) of patients had mediastinal metastases extending four or more levels. In the 55 patients with adenocarcinoma, one-level metastases were noted in only 35 percent (19/55) of patients, while 35 percent (19/55) had two-level metastases. Furthermore, there were 15 percent (8/55) and 16 percent (9/55) of patients who had extensive metastases in three or four or more levels, respectively. Adenosquamous carcinoma was diagnosed in only seven patients, but one-level metastases were noted in only two of these and three patients had metastases in two levels. The other two patients had metastases in three and four levels, respectively. In small-cell carcinoma, surgical intervention was attempted only for patients evaluated as

Table 2—Cell Types and Extent of Mediastinal Node Metastases

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Extent of Mediastinal Metastasis (Levels)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>31 (59)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>19 (33)</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>2 (39)</td>
</tr>
<tr>
<td>Small-cell carcinoma</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Large-cell carcinoma</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>58 (47)</td>
</tr>
</tbody>
</table>

*1, 2, 3 = mediastinal metastases were confined in 1, 2, or 3 levels, respectively; ≥4 = metastases extended over four or more levels; data represent the number of patients; numbers within parentheses are percentages.
having stage I or II preoperatively and patients with stage III were excluded. Thus, these six patients had metastatic mediastinal nodes confined within one or two levels. Two patients with large-cell carcinoma had metastases in one or two levels.

In total, 47 percent (58/124) of the patients had one-level mediastinal metastases, 29 percent (36/124) had two-level metastases, 12 percent (15/124) had three-level metastases, and 12 percent (15/124) had four or more levels involved.

**Effect of Primary Tumor Location on Nodal Metastases**

Table 3 shows the relationship between the location of the primary tumor and the level of nodal metastasis within the mediastinum. The location of metastatic lesions in the upper mediastinum and those in the lower mediastinum are separated by a dotted line. The 45 right upper lobe lesions had 88 metastatic foci (1.96 levels on average). Metastases in the upper mediastinum were most frequently noticed at levels 3a, 3, and 3p (73 percent [29/45]). In addition, 40 percent (18/45) of the metastatic foci occurred at level 2, 36 percent (16/45) at level 4, and 9 percent (4/45) at level 1. On the whole, there were 67 metastatic lymph foci (1.49 levels on average) within the regional mediastinum. This group also had nonregional nodal metastases in 36 percent (16/45) of cases at level 7, in 9 percent (4/45) at level 8, and in 2 percent (1/45) at level 9. There were 21 foci (0.47 levels on average) in the nonregional mediastinum in this group of patients.

When the same comparison was made concerning the 36 patients with right middle or lower lobe lesions, there were 74 metastatic foci (2.06 levels on average). Sixty-nine percent (25/36) of patients had regional mediastinal metastases at level 7, 11 percent (4/36) at level 8, and 6 percent (2/36) at level 9. In this group, there were 31 metastatic foci in the regional mediastinum (0.86 levels on average). Furthermore, in contrast to the right upper lobe group, there was a high incidence of metastatic foci to the upper or nonregional mediastinum. These were most frequently found in levels 3a, 3, and 3p (47 percent [17/36]). In addition, there were metastases to level 2 and level 4 in 31 and 28 percent, respectively. Furthermore, there was a right lower lobe cancer in which nodal metastases extended as far as level 1. There were 39 (1.08 levels on average) nonregional nodal metastases. This was more than were observed in the regional mediastinum, so that the 36 patients in this group showed a higher incidence of nonregional metastases than of regional metastases.

The 35 patients in the left upper lobe group had 67 metastatic foci (1.88 levels on average). Nodal metastases to the regional mediastinum were most frequently detected at level 5 (71 percent [25/35]) and level 6 (43 percent [15/35]). In 29 percent of cases (10/35) there were metastases at levels 3a, 3, and 3p and in 17 percent (6/35) there were metastases at level 4. Metastatic foci were absent at level 1 and present in 3 percent (1/35) at level 2. Nodal metastases to the regional mediastinum totaled 57 foci (1.63 levels on average). Nonregional nodal metastases were noted in 20 percent (7/35) of patients at level 7, in one patient (3 percent) at level 8, and in 6 percent (2/35) at level 9. There were ten metastatic foci to the nonregional mediastinum (0.29 levels on average). This figure was rather smaller than that observed with right lower lobe lesions (0.47 levels).

There were eight patients with left lower lobe lesions having 12 metastatic foci (1.5 levels on average).
Metastasis to the regional mediastinum was seen in 38 percent (3/8) at level 7, in 50 percent (4/8) at level 8, and in one patient (13 percent) at level 9. There were a total of eight metastatic foci in the regional mediastinum (1.0 level on average). Metastatic lesions in the upper mediastinum were detected at level 4 in one case (13 percent), at level 5 in one patient (13 percent), and at level 2 in two patients (25 percent). In total four metastases were seen in the nonregional mediastinum (0.5 levels on average).

The 124 patients had a total of 241 levels of mediastinal node metastases (1.94 levels on average). There were 171 nodes involved in the upper mediastinum (1.38 levels on average) and 70 nodes in the lower mediastinum (0.56 levels on average). The most frequent metastatic sites were levels 3a, 3, and 3p in 48 percent of the 124 patients. The second most prevalent site was level 7 where 41 percent (51/124) had metastases. About one fourth of the patients had metastatic foci at levels 2, 4, and 5. The incidence of metastases to levels 6 and 8 were 14 percent (17/124) and 10 percent (13/124), respectively. The least common metastatic sites were levels 1 and 9 that were involved in 4 percent and 5 percent of patients, respectively.

Comparison of Metastatic Patterns between Squamous Cell Carcinoma and Adenocarcinoma

Figure 2 shows a comparison of the frequency of nodal metastases in squamous cell carcinoma and adenocarcinoma to the regional and nonregional mediastinum. Eighty-eight percent (15/17) of squamous cell carcinomas in the right upper lobe (Fig 2, A) had...
nodal metastases to the regional upper mediastinum, whereas 35 percent (6/17) had nodal metastases to the nonregional mediastinum. All of the 15 left upper lobe lesions had regional nodal metastases, and twenty percent (3/15) had nonregional nodal metastases.

The 23 adenocarcinomas in the left upper lobe (Fig 2, B) had metastases to the regional mediastinum in 91 percent (21/23) of patients and there were nonregional nodal metastases in 35 percent (8/23). Ninety-two percent (12/13) of the left upper lobe tumors had metastases to the regional mediastinum and nonregional nodal metastases were present in 23 percent (3/13).

Squamous cell carcinomas in the right lower lobe (Fig 2, C) had metastatic foci to the regional mediastinum in 67 percent (10/15) of patients, while nonregional nodal metastases were present in 53 percent (8/15). The incidence of metastases to the regional compartment of the mediastinum was the least for squamous cell carcinoma in the right lower lobe among the four groups. Among five patients with left lower lobe squamous cell carcinomas, regional nodal metastases were found in 80 percent and there was one metastatic focus (20 percent) in the upper mediastinum.

Adenocarcinoma in the right lower lobe (Fig 2, D) had metastatic foci in the regional mediastinum in 88 percent (15/17) and had nodal metastases to the upper mediastinum in 47 percent (8/17). All three patients with primary tumors in the left lower lobe had regional metastases and there was one patient who had metastases in the upper mediastinum.

Frequency of Skip Nodal Metastases Outside the Regional Mediastinum

Table 4 shows the frequency of skip metastasis. Among the 45 right upper lobe lesions, there were five (11 percent) where skip nodal metastases were present without regional metastases. The 36 right lower lobe lesions had nine cases (25 percent) of skip metastases without regional involvement. The 35 left upper lobe lesions had two (6 percent) skip metastases. Among the eight cases of left lower lobe lesions, there was one case (13 percent) of skip metastasis to the upper mediastinum.

In total, there were 17 cases (14 percent) of skip nodal metastases to the nonregional compartment without regional metastasis. Ten cases were squamous cell carcinoma, five were adenocarcinoma, and there was one case each of small-cell carcinoma and mucoepidermoid carcinoma. Among 44 lower lobe lesions there were ten cases (25 percent) of skip metastases, whereas among 80 upper lobe lesions there were only seven cases (9 percent).

**Discussion**

For the surgical treatment of lung cancer, it is very important how primary lesions metastasize to the mediastinal lymph nodes and where the prevalent sites of nodal metastasis are. The lymph node map shown in Figure 1 was first proposed by Naruke et al2 and slight modifications were made thereafter. The Japan Lung Cancer Society has approved this map and it is in international use. In our Department, all of the mediastinal lymph nodes shown in this map were removed, including surrounding fatty tissues as a routine operative procedure for lung cancer and were pathologically examined.

As shown in Table 1, there were 540 patients who underwent curative resection for lung cancer with complete lymph node dissection among the 717 patients who had resection of lung lesions. Sixty-one percent of the 540 cases were N0, 16 percent were N1, and 23 percent were N2. These figures corresponded well to the report by Libshitz et al6 that 60 percent had N0, 16 percent had N1, and 24 percent had N2 disease among 200 cases of curatively resected lung cancer. It must be pointed out that this series included both macroscopically apparent N2 disease and microscopic N2 disease that was verified on postoperative histopathologic examination. Also it must be kept in mind that most of the cases in this series were of advanced hilar lung cancer. There were a total 105 advanced cases with T2, N2 (57 cases), T3, N2 (42 cases), and T4, N2 (six cases) disease that comprised 85 percent of the 124 patients. T1, N2 lesions accounted for 15 percent of the cases.

In this study, the mediastinum was divided into two compartments, the upper mediastinum and the lower mediastinum for comparison of the frequency of nodal metastases to the regional and nonregional mediastinum. Primary tumor location was also classified into two groups, i.e., upper lobe lesions and lower (plus middle on the right side) lobe lesions. It was found
that mediastinal node metastases could occur beyond the regional mediastinum. This was especially true in the case of lower lobe primary lesions. There were frequent nodal metastases in the upper mediastinum arising from lower lobe primary lesions, as can be seen in Table 2 and Figure 2. About half of the right middle/lower lobe squamous cell carcinomas and adenocarcinomas had nodal metastases to the upper mediastinum (Fig 2, C and D). Left lower lobe lesions had three metastases to the 5 and 6 lymph node levels. Libshitz et al6 also reported seven metastases to the ductal nodes, two of which were from left lower lobe primary tumors. In contrast, nodal metastases to the lower mediastinum from upper lobe primary lesions were present in about one third of patients (Fig 2, A and B).

There was a relatively high frequency of skip nodal metastases from the lower lobe to the upper mediastinum, as shown in Table 4. Also, it should be noted that there was a high incidence of metastases to the lower mediastinum from the upper lobe. There was a relatively high incidence of nodal metastases to the subcarinal (level 7) nodes from upper lobe primary lesions. Right upper lobe lesions produced subcarinal metastases in 36 percent of cases, and 20 percent of left upper lobe lesions had subcarinal metastases. Libshitz et al6 reported that there were 29 patients with metastases to the subcarinal nodes. Eleven patients had upper lobe cancers and five had left upper lobe cancer. In ten of these patients with upper lobe cancer, the mediastinal metastases were limited to the subcarinal lymph nodes. We also observed seven cases of skip nodal metastases to the subcarinal nodes from upper lobe lesions (five from the right upper lobe and two from the left upper lobe).

There were six patients with involvement of the pulmonary ligament nodes. The primary tumors in these patients were in the right upper lobe (one), the right lower lobe (two), the left upper lobe (two), and the left lower lobe (one), ie, half the patients with metastases to level 9 were from the upper lobe primary tumors. There were also six patients with metastases to the pulmonary ligament in the report of Libshitz et al6 and five of them were lower lobe cancers (four on the left and one on the right).

Martini et al1 reported that 22 of 32 survivors with N2 disease had lymph nodes involved at only one level and ten had diseased nodes at two or three levels. All of the above-mentioned reports and the results of the present study recommend the performance of extensive nodal dissection during lung cancer surgery. By performing extensive nodal dissection in the mediastinum, accurate postoperative staging can be accomplished.

According to the report of Martini et al,1 three mediastinal lymph node compartments are amenable to exploration and adequate dissection. They are the superior mediastinum by right thoracotomy, the subaortic region by left thoracotomy, and the subcarinal region and inferior mediastinum by either a right- or left-sided approach. Regarding right-sided cancer, there is usually no difficulty in performing complete nodal dissection of the above-mentioned three compartments. However, there are anatomic restrictions in the case of left-sided cancer. In fact, as can be seen in Table 3 and Figure 2, the frequency of nodal metastases to the left mediastinum was lower than to the right side. For complete lymph node dissection in these three compartments, our current procedure of nodal dissection after mobilization of the aortic arch followed by median sternotomy appears to be reasonable.4 As a result of using this procedure in 20 patients, metastatic involvement of mediastinal lymph nodes was histologically proven in four patients, all of which might not have been detected if these adjunctive methods had not been used.

Whether these operative procedures for extensive mediastinal lymph node dissection can improve the survival rate of the patients with N2 disease should be evaluated by a prospective study.

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