Re-evaluation of non-palpable scalene lymph node biopsy for the staging of non-small cell lung cancer

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Abstract

Objectives: The purpose of this study was to determine the most suitable candidates for scalene lymph node biopsy to detect non-palpable scalene lymph node metastasis (N3-scalene) in non-small cell lung cancer patients. Methods: Standard cervical mediastinoscopies and ipsilateral scalene lymph node biopsies were performed preoperatively by a single surgeon on 121 consecutive patients with non-small cell lung cancer scheduled to have surgical resection between January 1997 and August 2002, who had neither evidence of distant metastasis on imaging diagnosis nor palpable supraclavicular lymph nodes. Results: N3-scalene was detected in six patients (5.0%), who all had non-squamous cell carcinoma, including one (1.0%) out of 98 patients with negative standard cervical mediastinoscopy and five (21.7%) out of the remaining 23 patients with positive mediastinal lymph node involvement. There was a significant difference in the incidence of the N3-scalene between the two groups (P < 0.01). Five patients with N3-scalene had metastatic lesions in the multilevel mediastinal lymph node station on the same side as the cancer (multilevel N2), and accounted for 31.3% of 16 patients with multilevel N2 disease. The N3-scalene was detected in 5 (45.5%) of 11 patients with lung cancer classified as non-squamous cell carcinoma with multilevel N2 disease. Conclusions: The results of the present study suggest that non-palpable scalene lymph node biopsy is indicated for lung cancer patients diagnosed as having non-squamous cell carcinoma with mediastinoscopic multilevel N2 disease.

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1. Introduction

Although non-palpable scalene lymph node biopsies were once performed routinely for lung cancer staging, this procedure became less popular due to a very low metastasis-positive rate [1]. On the other hand, standard cervical mediastinoscopy is continuously being performed at the present time, because its metastasis-positive rate remains as high as 20–30% [2].

The presence of N3 disease was believed to indicate the unfeasibility of using a surgical approach. However, N3 diseases, including scalene lymph node metastasis, as well as N2 disease, in non-small cell lung cancer have been subject to recent clinical trials on induction chemotherapy or chemoradiotherapy followed by surgery [3–8].

In the present study, we tried to determine the most suitable candidates for scalene lymph node biopsy to detect non-palpable scalene lymph node metastasis (N3-scalene) in non-small cell lung cancer patients on the basis of analysis of the relationship between N3-scalene detected by scalene lymph node biopsy and the clinical characteristics, including the results of mediastinoscopic biopsy.

2. Material and methods

Standard cervical mediastinoscopies and ipsilateral scalene lymph node biopsies were preoperatively performed by a single surgeon on 121 consecutive patients with non-small cell lung cancer, scheduled to have surgical resection between January 1997 and August 2002, who had neither evidence of distant metastasis nor palpable supraclavicular lymph nodes. Distal metastasis was always evaluated by...
brain MRI, chest and upper abdominal CT, and bone scintigraphy. Positron emission tomography (PET) was not performed to evaluate lymph node metastasis.

2.1. Procedures for cervical mediastinoscopy and scalene biopsy

Each patient was placed in a supine position with posterior flexion of the neck. A sharp dissection was made in the midline through a 2–3 cm transverse suprasternal incision, to separate the cervical strap muscles and incise the pretracheal fascia. Digital dissection into the superior mediastinum was then made to conduct a standard cervical mediastinoscopy. Bilateral superior mediastinal (Naruke no. 1), paratracheal (no. 2), and tracheobronchial (no. 4) lymph nodes, as well as the pretracheal (no. 3) and subcarinal (no. 7) lymph nodes were biopsied. Successively, the skin incision was extended to the center of the sternocleidomastoid muscle on the tumor side, and then as much as possible of the inferomedial scalene fat pad, including the lymph node in which the anthracotic pigment was deposited, was removed according to the method of Maloney et al. [9].

2.2. Study items and statistical methods

The items examined are as follows: (1) clinical characteristics of the patients and their primary tumors, (2) precision of the mediastinoscopy, (3) relationship between the results of the scalene lymph node biopsy and those of the mediastinoscopy, (4) any relationship between the results of the scalene lymph node biopsy and age, sex, tumor size, tumor-occupying site, histopathological type of the tumor, or clinical stage, and (5) morbidity and mortality of the scalene lymph node biopsy.

The data obtained were statistically analyzed with a $\chi^2$-test (results of mediastinoscopy, sex, tumor occupying sites, histological types of the tumors, and clinical stages) or Student’s $t$-test (age and tumor sizes). A different level of $P < 0.05$ was considered significant.

3. Results

3.1. Patient and their primary tumor characteristics

The patients were 98 males and 23 females at 42–81 years of age, with a mean of 69 ± 11.3 years. The tumor size ranged from 1.0 to 9.8 cm, with a mean of 5.1 ± 3.3 cm. Tumor-occupying sites were: the right upper lobe in 44 patients, the right lower lobe in 26, the left upper lobe in 26, and the left lower in 25. The tumors were histologically classified as squamous cell carcinoma in 49 patients (central lesions in 16 cases and peripheral lesions in 33), adenocarcinoma in 60 (peripheral lesions in all cases), adenosquamous carcinoma in 5 (peripheral lesions in all cases), and large cell carcinoma in 7 (peripheral lesions in all cases). We defined the central lesions as lesions within the inner third of the lung parenchyma. Clinical stages were determined according to the international staging system, and were IA in 37 patients, IB in 31, IIA in 1, IIIB in 19, IIIA in 27, and IIIB in 6. Node involvement was determined to be $N_2$ in all the 27 IIIA, including nine bulky $N_2$ cases. Of the six IIIB patients, one was found to have non-bulky $N_2$ and five $N_0–1$ diseases, respectively (Table 1).

<table>
<thead>
<tr>
<th>Characteristics</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>98/23</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean 69</td>
</tr>
<tr>
<td></td>
<td>Range 42–81</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>Mean 5.1</td>
</tr>
<tr>
<td></td>
<td>Range 1.0–9.8</td>
</tr>
<tr>
<td>Location</td>
<td>Right upper: 44</td>
</tr>
<tr>
<td></td>
<td>Right lower: 26</td>
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<td></td>
<td>Left upper: 26</td>
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<tr>
<td></td>
<td>Left lower: 25</td>
</tr>
<tr>
<td>Histology</td>
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</tr>
<tr>
<td></td>
<td>Adeno: 60</td>
</tr>
<tr>
<td></td>
<td>Adenosquamous: 5</td>
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<tr>
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<td>Large: 7</td>
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<tr>
<td>Clinical stage</td>
<td>IA: 37</td>
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<tr>
<td></td>
<td>IB: 31</td>
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<tr>
<td></td>
<td>IIA: 1</td>
</tr>
<tr>
<td></td>
<td>IIIB: 19</td>
</tr>
<tr>
<td></td>
<td>IIIA (all $N_2$): 27</td>
</tr>
<tr>
<td></td>
<td>IIIB ($N_{0-1} 5$, $N_2 1$): 6</td>
</tr>
</tbody>
</table>

Squamous, squamous cell carcinoma; Adeno, adenocarcinoma; Adenosquamous, adenosquamous carcinoma; Large, large cell carcinoma.

3.2. Precision of mediastinoscopy

The results of mediastinoscopic biopsies were compared with postoperative histopathological findings of surgically resected lymph nodes in 105 patients, excluding 11 showing metastasis into the lymph nodes outside the reachable range of the mediastinoscope (Naruke nos 5, 6, 8, 9, and the lower part of no. 7) and five inoperable patients. Mediastinoscopy was determined to have a sensitivity rate of 0.90 (18/20), a specificity rate of 1.00 (85/85), and an accuracy rate of 0.98 (103/105).

3.3. Relationship between scalene node biopsy and mediastinoscopic biopsy

$N_3$-scalene was detected in 6 (5.0%) of the 121 patients simultaneously undergoing mediastinoscopy and scalene lymph node biopsies. It was found in only 1 (1.0%) of
98 patients with negative standard cervical mediastinoscopy, whereas it was found in 5 (21.7%) of the remaining 23 patients with positive mediastinal lymph node involvement (20 with N2 and three with contralateral N3 disease). There was a significant difference in the incidence of the N3-scalene between the two groups (P < 0.01): Five N3-scalene patients with positive mediastinal lymph node involvement exhibited ipsilateral multilevel mediastinal lymph node metastasis (multilevel N2), existing among 31.3% of 16 patients with multilevel N2 disease. However, the N3-scalene was not found in three patients with N3-contralateral (Table 2).

3.4. Relationship between N3-scalene and clinical characteristics

Clinical characteristics of the six patients with the N3-scalene are shown in Table 3. They were aged 55–69, with a mean age of 62.6 years. Three of them were male and three were female. The tumor sizes ranged from 3.2 to 8.2 cm, with a mean of 5.5 cm. Their tumors were all peripherally located in the right upper lobe in four patients, the right lower lobe in one, and the left upper lobe in one. N3-scalene cases were more frequent in the upper lobe than in the lower lobe. Five patients were histologically found to have adenocarcinoma, while one had large cell carcinoma. Clinical stages were determined to be T2N3(bulky)M0 in three patients, T2N1M0 in two, and T2N0M0 in one. As previously mentioned, five patients were mediastinoscopically found to have ipsilateral multilevel N2 disease. None of the six patients had the N3-contralateral or the upper mediastinal lymph node (No. 1) metastasis. Two to seven scalene lymph nodes were removed, with a mean of 4.0, and one or two of them having the evidence of metastasis, with a mean of 1.8.

Because the number of patients with the N3-scalene was as few as only six, no statistical differences in age, sex, tumor size, tumor-occupying site, histological type, or clinical stage (especially the presence of N2 or bulky N2 disease) were observed, when compared with patients showing negative scalene lymph node involvement.

However, if the comparison had been limited to patients with non-squamous cell carcinoma accompanied by mediastinoscopic multilevel N2 disease, N3-scalene was, in fact, detected as frequently as 5 (45.5%) of 11 patients.

3.5. Morbidity and mortality

None of the patients developed complications of the scalene lymph node biopsy, such as hematoma, lymphorrhea, wound infection, or phrenic nerve palsy. No mortality was observed.

4. Discussion

In recent years, combined modality therapies for the treatment of stage IIIB non-small cell lung cancer, including induction chemoradiotherapy followed by surgery, have been clinically investigated [3–8]. Although many contralateral N3 disease are included in these trials, the N3-scalene is usually not, probably because its prognosis is considered poor. However, there has been a clinical trial containing the N3-scalene patients [3], and the 3-year survival rate in these patients has been reported to be 35%. We think that patients with a non-palpable N3-scalene can also be included as subjects in these trials.

Positive rate of non-palpable scalene lymph node biopsies for lung cancer staging were reported to vary greatly, from 1 to 51% [10]. However, non-palpable scalene lymph node biopsies are no longer being performed at the present time, in contrast to mediastinoscopy. The reason for this is that the actual positive rate of this biopsy is
considerably low [1]. In fact, the positive rate in our present study was as low as only 5.0%. Thus non-palpable scalene lymph node biopsies should be limited to properly selected cases for lung cancer staging.

Lee and Ginsberg [11] simultaneously performed standard cervical mediastinoscopies and non-palpable scalene lymph node biopsies for lung cancer staging, and evaluated the relationship between the results of two diagnostic modalities. They found the N3-scalene disease in 32% of 58 patients with positive mediastinal lymph node metastasis, including 15.3% of patients with N2 disease and 68.2% of patients with contralateral N3 disease. However, the scalene lymph node biopsies detected no metastatic lesions in 23 patients who were macroscopically suspected of having metastatic lesions, although their frozen sections obtained under mediastinoscopy were negative for mediastinal lymph node metastasis. We also obtained similar results when these two examinations were simultaneously performed on 121 consecutive lung cancer patients. We have performed routine mediastinoscopy to evaluate lymph node metastasis in lung cancer patients because the accuracy of diagnostic imaging technique such as CT and/or MRI remains unsatisfactory and PET has no widespread use in Japan. The N3-scalene disease was observed in 21.7% of patients with positive mediastinal lymph node involvement, and this incidence was significantly higher than the 1.0% incidence found among patients with negative mediastinal lymph node metastasis. The five patients with the N3-scalene all had the multilevel N2 disease, existing among 31.3% of multilevel N2 patients. However, we failed to detect the N3-scalene in 3 patients with contralateral N3 disease.

In the present study, the relationship between clinical stages on imaging diagnosis, particularly N2 and bulky N2 disease, and the N3-scalene disease was not recognized. It has been pointed out that the rate of the N3-scalene is related to tumor location and histological type. Since Shatzlein et al. [12] detected the N3-scalene disease in 29% of patients with central non-squamous cell carcinoma, measuring 3 cm or more in diameter, they pointed out that a scalene lymph node biopsy should be indicated for lung cancer satisfying the above conditions. Lee and Ginsberg [11] also reported that 19 patients with N3-scalene disease had all central and non-squamous cell carcinoma. In our six N3-scalene patients, their primary lesions were all located peripherally, and were classified as a non-squamous cell carcinoma, including adenocarcinomas and large cell carcinoma. Although the frequency of N3-scalene disease may increase when the adenocarcinoma or large cell carcinoma, which usually occurs peripherally, extends centrally, it was revealed in the present study that the N3-scalene disease can exist, even if the tumor is localized peripherally. When the results of the mediastinoscopic biopsy were evaluated in combination with the histological findings of the tumor, it was determined that the N3-scalene existed at a high frequency of 45.5% among non-squamous cell carcinoma patients with multilevel N2 disease.

N3-scalene was detected in only 1% of 98 patients with negative mediastinoscopy. Because of this low positive rate, scalene lymph node biopsy was not useful for this group. On the other hand, N3-scalene existed at a high incidence of 31% in the patients with mediastinoscopic multilevel N2 disease. Since both N3-scalene and multilevel N2 disease are candidates for the same induction therapy, scalene lymph node biopsy to detect N3-scalene in multilevel N2 patients may be thought to be of little clinical value. However, several reports have suggested that postinduction resection may be indicated only for patients with pathologic downsizing of lymph node metastasis after induction therapy. Pathologic downsizing from N2 or N1 to N0/N1 has been shown to be one of most powerful predictors of survival after resection following induction therapy [3,6]. The clinical significance of scalene lymph node biopsy for detecting N3-scalene in multilevel N2 patients is to (1) determine the operative indication by ascertaining nodal downsizing after induction chemotherapy by re-mediastinoscopy and re-scalene lymph node biopsy, and (2) select the proper operative approach, e.g. median sternotomy, lung resection, and neck and mediastinal lymph node dissection.

We performed the scalene lymph node biopsies on the same side as the tumor. Brantigan et al. [10] noted in their paper that most of the lymphatic drainage of the left lower lobe crosses to the right side scalene lymph nodes. Therefore, right side scalene lymph node biopsy should be performed for all lesion of the right lung and left lower lobe. However, we performed left scalene lymph node biopsies for 25 patients with left lower lobe cancer. Because N3-scalene was not detected in any of these patients, we should have performed right scalene lymph node biopsies. It seems to be important for the accurate detection of N3-scalene disease, that the skin incision made for mediastinoscopy be extended 1 cm to both the right and left sides, to achieve a bilateral open scalene fat pad excision. We performed the ipsilateral open scalene fat pad excision without the development of related complications.

In the present study, mediastinoscopy showed satisfactory precision, compared with postoperative histopathological findings, with a sensitivity rate of 0.90, a specificity rate of 1.00, and an accuracy rate of 0.98. It is better to shift invasive diagnostic procedures such as mediastinoscopies or open biopsies, to non-invasive procedures, such as PET, to determine the presence of lymph node metastasis from histologically proven lung cancer. The studies on the correlation between mediastinal lymph node sampling with mediastinoscopy or thoracotomy and PET or PET combined with CT revealed that the diagnostic precision of these imaging diagnosis for the determination of the presence of lymph node metastasis has increased [13]. As a non-invasive technique, PET is expected to increase furthermore in diagnostic precision although there are still
problems to be solved, such as equipment distribution and insurance applications.

In conclusion, the results of the present study suggest that non-palpable scalene lymph node biopsy is indicated for lung cancer patients diagnosed as having non-squamous cell carcinoma with mediastinoscopic multilevel N2 disease. However, further studies should be performed due to small number of cases with the N3-scalene, single N2, or contralateral N3 disease in the present study.

References


