

Omission of Mediastinal Lymph Node Dissection in Lung Cancer: Its Techniques and Diagnostic Procedures

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To reduce or omit a mediastinal lymph node dissection in the patients with clinical stage I non-small cell lung cancer (NSCLC), several authors examined the prevalence of metastatic sites of lymph nodes. Because lymphatic drainage usually heads for the upper mediastinum in upper lobe cancer and for the lower mediastinum in lower lobe cancer, upper and lower mediastinal lymph node dissection could be reduced in lung cancers of lower lobe and upper lobe.

By using sentinel node (SN) navigation surgery, it is possible to omit mediastinal lymph node dissection. Radiological findings are also useful to determine reduction of mediastinal lymph node dissection. In clinical stage Ia adenocarcinomas that show ground glass opacity (GGO) findings on computed tomography (CT) or negative for fluorodeoxyglucose accumulation on positron emission tomography (PET), mediastinal lymph node dissection can be omitted, because these types of adenocarcinomas rarely metastasize to the lymph nodes. By using these procedures, mediastinal lymph node dissection can be reduced or omitted with little risk of local recurrence. (Ann Thorac Cardiovasc Surg 2006; 12: 83–8)

Key words: lung cancer, lymph node dissection, sentinel node, positron emission tomography, computed tomography

Introduction

Mediastinal lymph node dissection is a procedure used to secure complete local control of non-small cell lung cancer (NSCLC), with subsequent improvement in survival as well as nodal staging.¹⁻⁵⁾ However, how many patients with clinical stage I will be advantaged by mediastinal lymph node dissection? It has been stated that 20-25% of patients with clinical stage I disease have mediastinal lymph node metastases¹⁻⁵⁾ and that 20-25% of them

may be cured by mediastinal lymph node dissection.⁶⁾ Hence, only 5% of patients with clinical stage I disease may benefit from mediastinal lymph node dissection.

To minimize damage caused by mediastinal node dissection in patients with clinical stage I NSCLC, several authors examined the characteristics of lymphatic drainage, as well as the incidence of lymph node metastasis. This was undertaken with respect to the location of the primary tumor and it indicated the possibility of reduction in dissection of mediastinal lymph nodal stations. In 1960, Cahan reported that the upper mediastinal lymph nodes should be dissected for patients with upper lobe cancer and the lower mediastinal lymph nodes should be dissected for those with lower or middle lobe cancer.⁷⁾ Recently, the concept of Cahan has been revisited, and some authors have omitted dissection of lower and upper mediastinal lymph node stations in upper and lower lobectomy.⁸⁻¹¹⁾

To expand the possibility of reduction of mediastinal

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Table 1. Lymph node nomenclature

| Station | Name |
|----------------------|----------------------------------|
| Superior mediastinal | |
| 1 | Highest mediastinal ^a |
| 2 | Paratracheal ^a |
| 3 | Pretracheal ^a |
| 4 | Tracheobronchial ^a |
| Aortic | |
| 5 | Botallo ^a |
| 6 | Para-aortic ^a |
| Inferior mediastinal | |
| 7 | Subcarinal ^a |
| 8 | Paraesophageal ^a |
| 9 | Pulmonary ligament ^a |
| Hilar | |
| 10 | Hilar ^b |
| 11 | Interlobar ^b |
| 12 | Lobar ^b |
| Intrapulmonary | |
| 13 | Segmental ^b |
| 14 | Subsegmental ^b |

^a, N2 node; ^b, N1 node.

lymph node dissection, the availability of intraoperative sentinel lymph node (SN) biopsy has been examined, using radio-isotope mapping.¹²⁻¹⁷⁾

Here, we examine reduction of lymph node dissection of clinical T1N0M0 lung cancer via literature review.

Reduction of Mediastinal Lymph Node Dissection by the Localization of Lung Cancer

In 1999, Naruke et al. examined the incidence of lymph node metastasis in each lobe from the data of 1,815 patients with T1 NSCLC who had major lung resection with mediastinal lymph node dissection.⁸⁾ Table 1 shows the lymph node nomenclature used in the original lymph node map for lung cancer reported by Naruke et al.⁴⁾ They reported that, while the frequencies of metastases of hilar lymph nodes (#10-13) were almost same in each lobe, those of each mediastinal lymph node stations were dependent on the lobe; i.e. the usual metastatic sites of mediastinal lymph node in each lobe were as follows: right upper lobe, #3–12.3% (80/648) and/or #4–8% (52/648); right middle lobe, #3 or #7–16.4% (13/79); right lower lobe, #7–13.7% (13/79); left upper lobe, #5–12.3% (60/489); and left lower lobe, #7–11.9% (26/219). As based on these data, they concluded that, while hilar lymph nodes were usually SNs in lung cancer, the following mediastinal lymph nodes could be SNs: #3 and/or #4 in right

Table 2. Residual mediastinal lymph node metastasis in T1 patients with negative mediastinal lymph nodes (Naruke T et al., *Eur J Cardiothorac Surg* 1999; 16: S17–24)⁸⁾

| Lobe | Mediastinal SNs | Residual metastasis (%) |
|------|-----------------|-------------------------|
| RUL | #3 and/or #4 | 2/249 (0.8) |
| RML | #3 and/or #7 | 0/38 (0) |
| RLL | #7 | 5/147 (3.4) |
| LUL | #5 and/or #6 | 3/186 (1.6) |
| LLL | #7 | 3/75 (4.0) |

SN, sentinel node; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

upper lobe, #3 and/or #7 in right middle lobe, #7 in right lower lobe, #5 and/or #6 in left upper lobe, and #7 in left lower lobe. Therefore, they described that, in clinical T1N0M0 lung cancer, if the hilar lymph nodes and those mediastinal SNs were negative of metastasis by intraoperative pathological diagnosis, complete mediastinal lymph node dissection could be omitted with little risk of residual metastasis (Table 2). The other authors also reported similar results, i.e. (1) if the hilar and upper mediastinal lymph nodes were negative for metastasis in the upper lobe NSCLC, the lymph node dissection for lower mediastinum could be omitted; and (2) if the hilar and lower mediastinal lymph nodes were negative in the lower lobe NSCLC, the lymph node dissection for upper mediastinum could be omitted.^{9,18)} However, Asamura et al. described that #7 could be a SN in the left lingual lobe NSCLC.⁹⁾ Consequently, several institutions have already initiated selective mediastinal lymph node dissection for clinical T1N0M0 lung cancer.

Omission of Mediastinal Lymph Node Dissection by Sentinel Node Navigation Surgery

To reduce the scope of mediastinal lymph node dissection beyond selective lymph node dissection, SN navigation surgery has been performed.^{12,13,19,20)} In 2000, Liptay et al. reported the SN identification by using radioisotope with an 82% identification rate.¹²⁾ However, the previous reports using a radioisotope¹²⁻¹⁷⁾ were based on the data of ex vivo counting, i.e. evaluation of the radioactivity of the dissected lymph nodes; that is not practical in SN navigation surgery. Although ex vivo counting is more accurate than in vivo counting, SN identification before lymph node dissection by in vivo counting is necessary for SN navigation surgery.

In 2002, we reported the SN identification data in 46

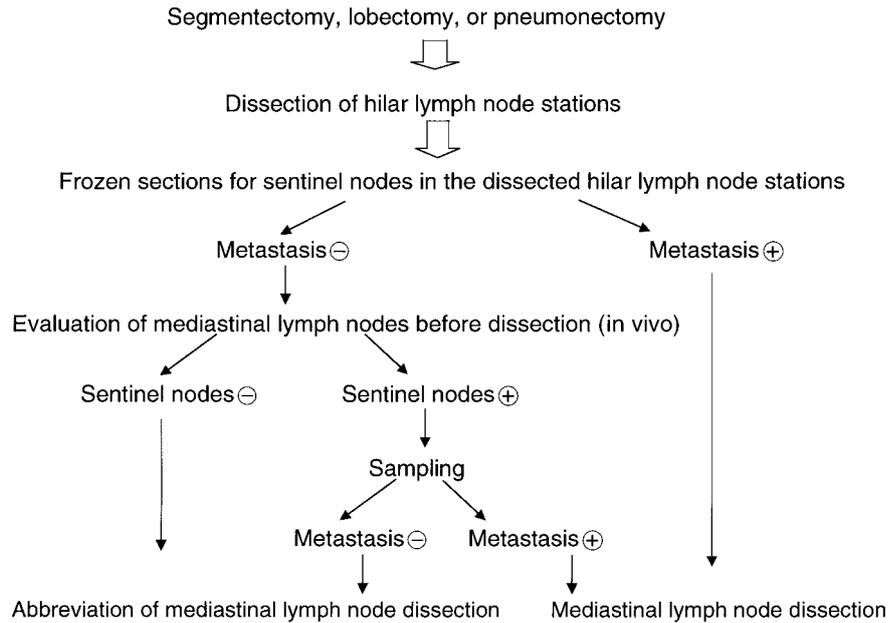


Fig. 1. The algorithm for omission of mediastinal lymph node dissection by using sentinel lymph node identification. The peak of the histogram is at the low CT number.

patients with clinical stages I-III NSCLC, with the following results: (1) there were no false negative SNs identified by ex vivo counting for patients with N1 or N2 disease, and (2) although the SN identification with in vivo counting was not available in hilar lymph node stations due to shine-through from the tumor radio-activity, it might be available for the mediastinum because there was less effect of radio-activity from the primary tumor.¹¹⁾ In 2004, we reported the results of in vivo identification of SN for 104 patients with clinical stage I NSCLC;²⁰⁾ results were as follows: (1) SNs could be identified in 84 patients (81%); (2) SNs were identified at the hilum by ex vivo counting in 78 of the 84 patients (93%) and at the mediastinum by in vivo counting in 40 patients (48%). While the in vivo counting of the mediastinum showed some false positive (over diagnosis) for SN identification, it missed (false negative) the mediastinal SNs only in 4 of the 84 patients (5%). From these results, we concluded that mediastinal lymph node dissection could be omitted by the algorithm in Fig. 1. First, patients with clinical stage I peripheral type NSCLC can be candidates for sentinel navigation surgery. To identify SNs in the hilar lymph node stations, segmentectomy or greater resection is necessary. Because the in vivo counting is not available for hilar lymph node stations, their SN identification is conducted by ex vivo counting after separating from the resected lung. The hilar SNs are examined in

intraoperative frozen sections. If the frozen section of hilar SNs showed metastases, a mediastinal lymph node dissection should be performed because of the high possibility of N2 disease. If it did not show metastasis, the mediastinal SNs are identified before lymph node dissection by in vivo counting. If there were no SNs in the mediastinum by in vivo counting, a mediastinal lymph node dissection can be omitted. If the in vivo counting of the mediastinum showed SNs, they are sampled for frozen sections. If a frozen section of mediastinal SNs did not show metastasis, the sampling is adequate and a mediastinal lymph node dissection can be omitted. If the frozen section showed metastasis, the mediastinal lymph node dissection should be performed. The study showed that N2 disease was shown in 9 of 84 (11%) patients who were diagnosed as N0 in computed tomography (CT) scan and that overlooking the mediastinal SNs by in vivo counting was shown in 4 of 84 patients (5%), resulting in the risk of leaving metastatic lymph nodes in the mediastinum to be 0.55% (11%×5%). We believe that this is an acceptable risk in the reduction of mediastinal lymph node dissection in the patients with stage I NSCLC.

Omission of Mediastinal Lymph Node Dissection for Stage I Squamous Cell Carcinoma

A skip metastasis, i.e. metastasis to the mediastinal lymph

Table 3. Correlation between pathological tumor stage and histogram pattern in clinical T1N0M0 lung adenocarcinomas

| Tumor stage | Histogram pattern | | | Total |
|-------------|-------------------|-----------------|-----------|-------|
| | One peak (low) | One peak (high) | Two peaks | |
| T1N0M0 | 18 | 34 | 27 | 80 |
| T1N1M0 | 0 | 4 | 0 | 4 |
| T2N1M0 | 0 | 3 | 0 | 3 |
| T1N2M0 | 0 | 7 | 1 | 7 |
| T2N2M0 | 0 | 1 | 0 | 1 |
| T3N2M0 | 0 | 1 | 0 | 1 |
| T4N0M0 | 0 | 3 | 0 | 3 |
| T4N1M0 | 0 | 1 | 0 | 1 |
| Total | 18 | 54 | 28 | 100 |

node without hilar lymph node metastasis, is one of the difficulties for omission of mediastinal lymph node dissection. The skip metastasis is usually encountered in adenocarcinomas. It has been reported that approximately 25% of adenocarcinomas with N2 or N3 disease are skip metastases.²¹⁾ However, the skip metastasis has been reported to rarely occur in T1 squamous cell carcinomas. Sakurai et al. reported that, while 19 of 70 patients (25%) with squamous cell carcinoma less than 3 cm had lymph node metastasis, none of them had skip metastases.²²⁾ Besides, Asamura et al. reported that lymph node metastasis was seen in only one of 16 patients (6%) with squamous cell carcinoma less than 2 cm.²¹⁾ From their reports, it could be stated: (1) mediastinal lymph node dissection could be omitted in squamous cell carcinomas less than 3 cm, if the intraoperative frozen section of hilar lymph nodes had no metastasis; and (2) mediastinal lymph node dissection could be omitted for patients with squamous cell carcinoma less than 2 cm.

Omission of Lymph Node Dissection from the CT Findings of Primary Tumor

Because lung adenocarcinomas showing ground glass opacity (GGO) by CT are usually pathological N0 disease,²³⁻³¹⁾ they are good candidates for omission of mediastinal lymph node dissection. By using the CT number histogram, we examined lymph node metastasis in GGO or solid lesions in 100 patients with clinical T1N0M0 adenocarcinomas. According to the CT number histograms, 18 patients had one peak at a low CT number (pure GGO), 54 had one peak at a high CT number (solid), and the remaining 28 had two peaks at both low and high CT numbers (mixed GGO) (Table 3).

Pathological TNM showed that all (100%) of the 18 adenocarcinomas with one peak at a low CT number were T1N0M0, and 27 of the 28 (96%) ones with two peaks were T1N0M0. While 34 of the 54 (63%) adenocarcinomas with one peak at a high CT number were pathological T1N0M0, but the remaining 20 (37%) had lymph node metastasis. Lymph node dissection could be omitted for adenocarcinomas with pure GGO and probably ones with mixed GGO, which were defined from CT number histograms.

Omission of Lymph Node Dissection from the Findings of Positron Emission Tomography (PET)

According to the meta-analysis by Dwamena et al., ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) has higher sensitivity and specificity than CT.³²⁾ However, PET cannot detect small or micro-metastasis because of lower limits of spatial resolution of a PET camera. We previously reported the size of metastatic foci yielding false negative lymph node staging with PET in patients with lung cancer.³³⁾ From the results of 564 lymph node stations in 80 patients with peripheral type lung cancer, the sizes of metastatic foci within lymph nodes that showed false-negative (n=8) and true-positive (n=28) with PET ranged from 0.5 to 9 mm (3 ± 1 mm) and from 4 to 18 mm (10 ± 3 mm), respectively ($p < 0.001$) (Fig. 2). None of the metastatic foci smaller than 4 mm could be detected with PET scanning. Therefore, lymph node dissection cannot be omitted for patients who are diagnosed N0 disease by PET scanning.

It has been reported that low grade lung cancers, such as carcinoid, mucoepidermoid carcinomas, and bronchioloalveolar carcinomas, usually show false-negative by PET

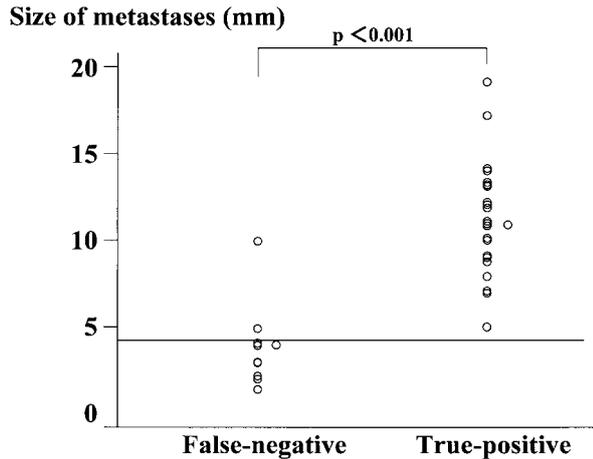


Fig. 2. The distribution of sizes of metastatic true-positive and false-negative lymph nodes with PET scan.

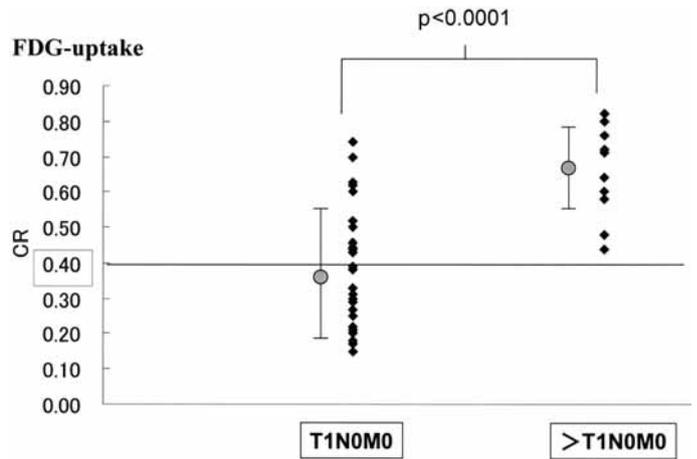


Fig. 3. The distribution of FDG-uptake of pathological T1N0M0 and more advanced stages than T1N0M0 in clinical T1N0M0 adenocarcinomas.

FDG, ¹⁸F-fluorodeoxyglucose; CR, contrast ratio.

scanning. We examined the correlation between lymph node metastasis and FDG-uptake in primary tumors, finding that FDG-uptake in primary tumor could predict lymph node metastasis in lung adenocarcinomas with clinical T1N0M0.³⁴⁻³⁶ FDG-uptake was evaluated by contrast ratio (CR) comparing with the FDG-uptake of contralateral lung. The correlation between the CR of the primary tumor and pathological stage in 52 lung adenocarcinomas with clinical T1N0M0 showed that, while all of the tumors with CR less than 0.4 were pathological T1N0M0, all of the tumors advanced more than T1N0M0 (n=11) showed CR higher than 0.4 (Fig. 3). Therefore, we concluded that lymph node dissection or mediastinoscopy could be omitted for adenocarcinomas with clinical T1N0M0 showing CR less than 0.4 on PET scanning.

While the standard operation for lung cancer is lobectomy and mediastinal lymph node dissection, we consider that mediastinal lymph node dissection may be omitted with use of techniques described.

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