Recurrence of mediastinal node cancer after lobe-specific systematic nodal dissection for non-small-cell lung cancer

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Abstract

OBJECTIVES: The standard surgical treatment for patients with non-small-cell lung cancer (NSCLC) is lobectomy with systematic nodal dissection (SND). Lobe-specific patterns of nodal metastases have been recognized, and lobe-specific SND (L-SND) has been reported. We performed L-SND depending on patient-related factors, such as age or the presence of diabetes or respiratory dysfunction, or in the context of specific tumour-related factors, such as the presence of a tumour with a wide area of ground-glass opacity.

METHODS: Between September 2002 and December 2008, 335 consecutive patients with clinical and intraoperative N0 NSCLC underwent curative lobectomies at Shizuoka Cancer Center Hospital. Among these 335 patients, 206 underwent SND (Group A) and 129 underwent L-SND. Of the 129 patients undergoing L-SND, 98 underwent L-SND due to patient-related factors (Group B) and 31 underwent L-SND due to tumour-related factors (Group C).

RESULTS: There were no significant differences in morbidity or blood loss between patients undergoing SND or L-SND, but there was a significant difference in the mean operative times. The 5-year disease-free survival (5-DFS) and 5-year overall survival (5-OS) of patients in Group C were 100%. Although the patients in Group B showed no significant difference in 5-DFS and 5-OS compared with Group A, patients in Group B had significantly more initial recurrence of mediastinal node cancer than did the Group A patients ($P = 0.0050$).

CONCLUSIONS: The recurrence of mediastinal node cancer in patients undergoing L-SND was significantly greater than that in those undergoing SND.

Keywords: Lung cancer • Lymph node dissection • Lobectomy

INTRODUCTION

The standard surgical treatment for patients with non-small-cell lung cancer (NSCLC) is lobectomy or pneumonectomy with systematic nodal dissection (SND) [1–3]. SND has been reported to be important for survival as well as for disease staging [2, 3]. However, the effect of SND on patient prognosis remains controversial.

Lobe-specific patterns of nodal metastases are now recognized owing to the increased analysis of the lymph node metastatic pathway [4, 5]. Some reports [4–6] have stated that right upper lobe tumours and left upper segment tumours tend to metastasize to the superior mediastinum, but rarely metastasize to the subcarinal nodes without concomitant metastasis to the hilar or superior mediastinal nodes. In addition, Okada et al. [5] reported that lower lobe tumours seldom metastasize to the superior mediastinal nodes without concomitant metastasis to the hilar or subcarinal nodes. Considering the results of the lobe-specific patterns of nodal metastases, the strategy of nodal dissection has been changing. As a result, lobe-specific SND (L-SND) has been developed [6–9].

PATIENTS AND METHODS

Between September 2002 and December 2008, 358 consecutive patients underwent lobectomy for clinical and intraoperative N0 NSCLC at Shizuoka Cancer Center Hospital. An intraoperative identification of disease was based on the surgeon's impressions or an intraoperative histological examination, or both. None of the patients received neoadjuvant therapy. Patients with multiple primary lung cancers ($n = 3$) or positive pleural lavage cytology ($n = 12$) were excluded. Complete resection was defined as cancer-free surgical margins, determined both grossly and histologically; 8 patients had incomplete resections. The remaining 335 eligible patients were investigated in this study.

Preoperative staging

All patients with NSCLC were clinically staged using 5-mm slice computed tomography (CT) scans of the chest and upper abdomen. In addition, the main tumour was evaluated before

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the operation to estimate the extent of ground-glass opacity (GGO) by thin-section helical CT scans, with 1-mm collimation. We suspected that large lymph nodes (>10 mm in the shortest axis) were positive for metastasis in the CT scans. Enhanced magnetic resonance imaging and 2-[18]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET) of the brain were routinely used for staging resectable tumours. We categorized lymph nodes according to the International Association for the Study of Lung Cancer (IASLC) map [10]. Disease stages were determined on the basis of the 7th TNM classification [11].

Lobe-specific systematic nodal dissection (Groups B and C)

The standard surgical treatment for NSCLC is lobectomy with SND [12], and it was performed on the 206 patients who were not at severe risk (Group A). We performed L-SND for 98 patients due to the presence of patient-related risk factors (Group B). These risk factors included advanced age and severe diabetes, respiratory dysfunction or cardiovascular disease (Table 1). On the other hand, we also performed intentional L-SND for 31 patients due to the presence of tumour-related factors (Group C). The tumour-related factors included the presence of a tumour with a maximum diameter of consolidation as a proportion of the maximum tumour diameter (consolidation/tumour ratio, C/T ratio) of <0.5, indicating a tumour with a wide area of GGO [13, 14], without strong uptake on FDG-PET (maximum standardized uptake value [SUV_{max}] <2.5), and the elevation of serum tumour markers. Data collection and analyses were approved by the institutional review board in 2009.

Surgical technique

In the SND group, lobe resection was combined with a radical systematic *en bloc* mediastinal lymph node dissection, as described by IASLC [12]. In the L-SND groups, lymph node dissection was performed on the basis of lobe-specific lymph node metastasis patterns. When the tumour was located in the right upper lobe, the upper mediastinal lymph nodes (upper and lower paratracheal nodes) and hilar lymph nodes were systematically removed. When the tumour was located in the left upper lobe, the aortopulmonary window nodes, aortic nodes, tracheobronchial nodes and hilar lymph nodes were systemically

Table 1: The risk factors of patients who underwent lobe-specific SND due to patient-related factors (Group B); patients may have exhibited more than one risk factor

Risk factor	Number
Respiratory dysfunction	37
Advanced age (>75 years)	27
Cardiovascular disease	17
Diabetes	17
Cerebrovascular disease	16
Hepatic dysfunction	4
Renal dysfunction	1

removed. In these cases, dissection of the lower mediastinum was not performed when the nodes in the hilum and the upper mediastinum or aortic nodes were free from metastases, as shown by intraoperative diagnosis. Intraoperative frozen section analyses were performed when lymph node metastases were suspected of being positive. On the other hand, when the tumour was located in a lower lobe, the subcarinal, lower mediastinal nodes and hilar lymph nodes were dissected; dissection of the superior mediastinum was omitted when the intraoperative diagnosis was negative.

Survival analysis

The length of overall survival (OS) was defined as the interval between the date of the surgical intervention and death due to any cause or the last follow-up visit. Observations were censored at the last follow-up when the patients were alive or subsequently lost to follow-up. The date of recurrence was defined either as the date on which histological proof of recurrent cancer was obtained or as the date on which positive clinicoradiological findings were obtained. The length of the recurrence-free period was calculated from the date of surgical intervention to the initial recurrence or the last follow-up visit. For the calculation of disease-free survival (DFS), patients who died without recurrence or who were known to not have recurrence on the date of their last contact were censored.

Statistical analysis

The cumulative OS and recurrence-free survival rates were estimated using the Kaplan–Meier method. Comparisons between groups were performed using the log-rank test. The analyses were performed with the JMP statistical software (version 9, SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics (Group A and B) are summarized in Table 2. The median follow-up time was 60 (range, 36–110) months. Table 3 presents the comparison of patients undergoing SND and L-SND with respect to their morbidities, operative times and blood losses. There was no significant difference in morbidity ($P = 0.1328$). The level of arrhythmia in SND patients was greater than that in patients undergoing L-SND, but the difference was not significant ($P = 0.0817$). The operative time in patients who underwent L-SND was shorter than that for patients undergoing SND ($P = 0.0005$). None of the patients died within 30 days of surgery.

Groups A and B

The 98 patients who underwent L-SND (Group B) were chosen for that procedure because of the presence of patient-related risk factors. Understandably, these patients had more risk factors than did the patients in Group A. Patients in Group B were significantly older ($P < 0.0001$) and had significantly lower 1-s forced expiratory volumes. On the other hand, these two groups of patients did not demonstrate any significant differences

Table 2: Patient characteristics (Groups A and B)

	Group A (N = 206)	Group B (N = 98)	P-value
Age (years)	64 (20–81)	70 (43–89)	<0.0001
Sex			
Male	115 (55.8%)	55 (56.1%)	0.71
Female	95 (44.2%)	43 (43.9%)	
Histology			
Ad	158 (76.7%)	65 (66.3%)	0.15
Sq	26 (12.6%)	20 (20.4%)	0.083
Others	22 (10.7%)	13 (13.3%)	0.51
Smoking index	145 (0–2500)	355 (0–4500)	0.15
FEV 1.0	2.245 (0.99–4.65)	2.06 (1.06–3.53)	0.0019
FEV 1.0%	76.25 (45.6–95.5)	73.95 (39.1–100.0)	0.0054
%VC	108.6 (69.2–142.9)	104.2 (73.2–152.5)	0.12
Tumour size (cm)	2.5 (0.7–6.0)	2.2 (0.9–10.0)	0.21
CEA (ng/ml)	2.5 (0.5–23.8)	2.7 (0.6–73.3)	0.87
SUV_{max} on PET	5.0 (1.0–25.3)	3.9 (0.88–28.0)	0.085
C/T ratio			
≥0.5	196 (95.1%)	92 (93.8%)	0.65
<0.5	10 (4.9%)	6 (6.2%)	
C-stage			
Stage I	196 (95.1%)	88 (89.8%)	0.084
Stage II	10 (4.9%)	10 (10.2%)	
pN0	173 (84.0%)	86 (87.6%)	0.38
pN1	17 (8.3%)	8 (8.2%)	0.98
pN2	16 (7.7%)	4 (4.1%)	0.21

Ad: adenocarcinoma; Sq: squamous cell carcinoma; C/T ratio: the maximum diameter of tumour consolidation as a proportion of the maximum tumour diameter (consolidation/tumour ratio); FEV: forced expiratory volume; CEA: carcinoembryonic antigen; SUV_{max}: maximum standardized uptake volume; PET: positron emission tomography; VC: vital capacity.

Table 3: Morbidity and invasiveness

	SND (N = 206)	L-SND (N = 129)	P-value
Morbidity	39	19	0.32
Arrhythmia	20	6	0.082
Chylothorax	6	3	0.74
Prolonged air leakage	3	4	0.31
Pneumonia	3	3	0.56
Cerebral disorder	3	1	0.57
Renal dysfunction	3	0	0.087
Emphysema	2	2	0.64
Peptic ulcer	2	1	0.85
Recurrent nerve paralysis	1	1	0.74
Bronchiopleural fistula	1	0	0.32
ARDS	0	1	0.17
Blood loss (g)	85.5 (0–630)	70.0 (0–611)	0.89
Operative time (min)	250 (114–433)	221 (113–567)	0.00050

ARDS: acute respiratory disease syndrome; SND: systematic nodal dissection; L-SND: lobe-specific systematic nodal dissection.

in tumour-related factors, such as their histological factors, carcinoembryonic antigen (CEA) levels or tumour sizes. In addition, there were no significant differences in the patients' pathological

N factor (Table 2). The 5-year disease-free survival rates (5-DFS) in Groups A and B were 77.7 and 76.4% (P = 0.6067), respectively (Fig. 1A). The 5-year overall survival (OS) rates in Groups A and B were 89.7 and 86.6% (P = 0.5259), respectively (Fig. 1B).

Group C

Thirty-one patients underwent L-SND because of the presence of specific tumour-related factors (Table 4). The median tumour size was 20 (range 10–40) mm. The SUV on ^{18}F-FDG PET was 1.43 (range 0.88–2.25). These patients had a mean serum CEA level of 1.8 (range 0.6–7.3) mg/dl, and all had N0 disease. Both the 5-DFS and the 5-OS rates in Group C patients were 100%.

Recurrence patterns

The recurrence patterns of the three groups are presented in Table 5. There was a significant difference in the initial recurrence of mediastinal node disease between Groups A and B (P = 0.0050). Eleven patients in both groups had initial recurrence in the mediastinal node; 7 (63.6%) of them had not only recurrences of mediastinal node, but also distant metastasis. Four patients, from both groups, had initial recurrence only in the mediastinal node (Table 6). All patients with metastasis in the mediastinal node underwent radiation therapy, followed by chemotherapy. One patient died of brain metastasis 10 years after surgery. The duration from initial recurrence to secondary recurrence was 11–44 months.

DISCUSSION

The standard surgical treatment for patients with NSCLC is lobectomy or pneumonectomy, with SND. However, the effect of mediastinal lymph node removal on survival is controversial. To date, a number of prospective studies for the assessment of SND have been performed. Previous reports [15–17] of randomized trials comparing SND with sampling have yielded inconsistent results, leaving the question of whether or not SND improves survival unresolved. Lymph node assessment by SND is also important for the accurate staging of NSCLC. Even peripheral small lung cancers of <2 cm show hilar and mediastinal node metastases with an incidence of >20% [9, 18]. In addition, N2 lung cancer, without N1 involvement, has an incidence of 27–38% [19–21]. If patients do not undergo SND, their evaluation is less complete than if the mediastinal node is evaluated. Recently, several studies [22, 23] have also reported that patient prognosis improves if they receive adjuvant chemotherapy. For example, meta-analysis showed that cisplatin-based chemotherapy significantly improved the survival of patients with NSCLC [23]. If the assessment of the mediastinal lymph node is not accurate, the patients who require adjuvant chemotherapy may not be correctly diagnosed and may not receive timely, appropriate treatment.

On the other hand, several investigators [4–6] have reported the identification of distinct patterns of metastatic spread through the lymphatic system, which are dependent on the location of the primary tumours. Asamura *et al.* [4] reported that tumours of the right lower lobe, with superior mediastinal metastasis, were associated with a particularly poor 5-year survival
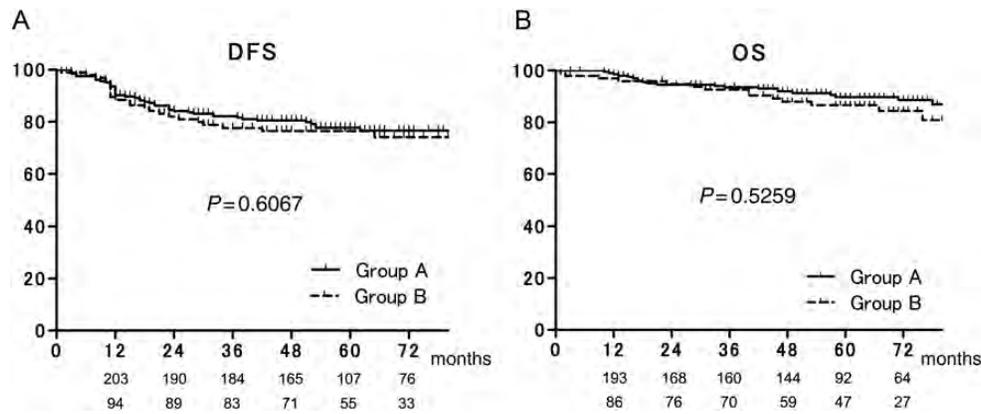
Figure 1: The 5-year disease-free survival rates (5-DFS) in Groups A and B were 77.7 and 76.4% (*P* = 0.6067), respectively (**A**). The 5-year overall survival (OS) rates in Groups A and B were 89.7 and 86.6% (*P* = 0.5259), respectively (**B**).

Table 4:   Patient characteristics (Group C)

	Group C (N = 31)
Tumour size(cm)	2.0 (1.0–4.0)
CEA(ng/ml)	1.8 (0.6–7.3)
SUV_{max} on PET	1.43 (0.88–2.25)
C/T ratio (<0.5/≥0.5)	31/0
pN0	31
pN1–2	0

C/T ratio: a tumour with a maximum diameter of consolidation as a proportion of the maximum tumour diameter (consolidation/tumour ratio).

Table 5:   Disease recurrence patterns

	Group A (N = 206)	P-value	Group B (N = 129)
All recurrences	46		24
Local	20	0.68	11
Distant	20		9
Local + distant	5		2
Lymph node recurrence	3	0.0050	8
Only mediastinal node	1	0.078	3

rate of 4.1%. Aokage *et al.* [6] reported that upper lobe tumours, with subcarinal metastasis, were also associated with a poor 5-year survival of 9.1%. Studies of dissection-SND have reported the examination of metastatic lymphatic spread and its prognosis [6–9].

However, there have only been two reports comparing L-SND with SND [7, 8] (Table 7). Okada *et al.* [7] performed SND in 377 patients between 1985 and 1996 and L-SND in 358 patients between 1997 and 2002 and reported that L-SND for Stage I NSCLC was as effective as SND. They also reported that morbidity of the patients undergoing L-SND was less than that of those undergoing SND. In addition, the pattern of recurrence was not significantly different between the two groups. Ishiguro *et al.* [8] compared L-SND for resectable NSCLC with SND, using propensity scores. They reported that L-SND did not worsen the survival of patients with NSCLC. However, they did not investigate tumour recurrence. Thus, neither of the two previous reports demonstrated a significant difference in either the 5-DFS or the 5-OS between SND and L-SND.

In this study, patients who underwent SND experienced a longer operative time than did those who underwent L-SND. A previous report [7] also stated that patients undergoing L-SND demonstrated significantly less morbidity than did those undergoing SND. SND may cause injury to the bronchial artery, recurrent nerve, thoracic duct or lymphatic flow, resulting in ischaemic changes [24] as well as hoarseness or chylothorax. In order to avoid such injuries, we performed palliative L-SND on

certain patients after considering their relevant risk factors. Even for such high-risk patients, palliative L-SND did not significantly affect patient survival compared with SND, raising our confidence that L-SND is effective, depending on patient-related factors. This is important, as high-risk patients do not receive adjuvant chemotherapy, even if they have pathological N2 tumours.

The investigation of mediastinal node tumour recurrence is very interesting. Three patients had initial recurrence of mediastinal node disease after SND, whereas 8 experienced mediastinal node recurrence after L-SND. However, 7 (63.6%) of the 11 patients not only had recurrence in the mediastinal node, but also demonstrated distant metastases. Four patients with SND had recurrence in mediastinal nodes only. Disease recurrence only in the mediastinal node occurred in 1 patient with SND and in 3 who underwent L-SND. From these results, lobectomy with SND appears to be the most effective treatment. The recurrence of mediastinal node tumours after L-SND or SND also indicated that the disease spreads systemically because 3 patients experienced secondary disease recurrence after radiation therapy for the initial recurrence of mediastinal node disease.

Minimally invasive surgery has been investigated for the treatment of thoracic malignancies. Some reports have promoted approaches that involve less of the pulmonary parenchyma, such as segmentectomy or wedge resection, for small lesions or those with GGO [12]. In our department, we do not perform limited surgery for patients with GGO lesions, but conduct lobectomies because of the size or location of the tumours. Metastatic nodes

Table 6: Four cases with only mediastinal node recurrence

Case	c-TNM	Surgery	Inoperative sampling	P-TNM	Initial	Secondary
70 women Ad	T1bN0M0	RLL L-SND	#4R; negative	T1aN0M0	2R, 4R, 11s (13 months)	Supraclavicular LN (25 months)
43 men Ad	T1aN0M0	LUL L-SND	None	T1aN0M0	2R, 7, 9, 11 (12 months)	Bone and brain (56 months)
50 women Ad	T1aN0M0	LLL L-SND	#5; negative	T2aN2M0	4L, 7 (7 months)	Lung (43 months)
51 men Ad	T1aN0M0	LUL SND	None	T1aN0M0	4L (62 months)	None

Ad: adenocarcinoma; RLL: right lower lobectomy; LUL: left upper lobectomy; LLL: left lower lobectomy; initial: initial site of recurrence; secondary: secondary site of recurrence.

Table 7: Previous reports of studies comparing SND and L-SND

	Patients	Number	Morbidity		5-year OS		Recurrence MN
Okada *et al.* [7]	Stage I	SND:377 L-SND:358	62 (17.3%) 38 (10.1%)	P = 0.005	79.7% 83.2%	P = 0.149	6 (1.6%) 7 (2.0%)
Ishiguro *et al.* [8]	Stages I–III	SND:625 L-SND:147	NA	NA	71.9% 76.0%	P = 0.29	NA
Our study	s-N0	SND:206 L-SND:129	39 (18.9%) 19 (14.7%)	P = 0.32	89.74% 86.61%[a]	P = 0.54	1 (0.48%) 3 (2.3%)[a]

NA: not available; OS: overall survival; recurrence MN: recurrence in mediastinal node; s-N0: surgical N0.
[a]L-SND depending on patient-related factors (*n* = 98).

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were uncommon in the patients in this study, and we performed lobectomies with sampling or intentional L-SND. The 5-DFS of patients undergoing L-SND due to tumour-related factors in this study was 100%. In these patients, L-SND may be overly invasive and sampling may have been proper.

There have been few reported comparisons of L-SND and SND, and randomized trials to compare these procedures have not been conducted. However, considering the previous reports on lymphatic spread, we believe that L-SND has already been established as an appropriate surgical treatment. In previous reports comparing L-SND with SND, L-SND has not resulted in poorer survival compared with SND [8, 9]. Although L-SND in high-risk patients did not have a significant effect on survival compared with SND, we paid close attention to the possibility of recurrence in patients undergoing L-SND.

CONCLUSION

The level of recurrence of mediastinal node disease in patients undergoing L-SND was significantly higher than that for those undergoing SND.

Conflict of interest: none declared.

REFERENCES

[1] Cahan WG. Radical lobectomy. J Thorac Cardiovasc Surg 1960;39: 555–72.

[2] Naruke T, Goya T, Tsuchiya R, Suemasu K. The importance of surgery to non-small cell carcinoma of lung with mediastinal lymph node metastasis. Ann Thorac Surg 1988;46:603–10.

[3] Martini N, Flehinger BJ, Zaman MB, Beattie EJ Jr. Results of resection in non-oat cell carcinoma of the lung with mediastinal lymph node metastases. Ann Surg 1983;198:386–97.

[4] Asamura H, Nakayama H, Kondo H, Tsuchiya R, Naruke T. Lobe-specific extent of systematic lymph node dissection for non-small cell lung carcinomas according to a retrospective study of metastasis and prognosis. J Thorac Cardiovasc Surg 1999;117:1102–11.

[5] Okada M, Tsubota N, Yoshimura M, Miyamoto Y. Proposal for reasonable mediastinal lymphadenectomy in bronchogenic carcinomas: role of subcarinal nodes in selective dissection. J Thorac Cardiovasc Surg 1998; 116:949–53.

[6] Aokage K, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Subcarinal lymph node in upper lobe non-small cell lung cancer patients: is selective lymph node dissection valid? Lung Cancer 2010;70:163–7.

[7] Okada M, Sakamoto T, Yuki T, Mimura T, Miyoshi K, Tsubota N. Selective mediastinal lymphadenectomy for clinico-surgical stage I non-small cell lung cancer. Ann Thorac Surg 2006;81:1028–32.

[8] Ishiguro F, Matsuo K, Fukui T, Mori S, Hatooka S, Mitsudomi T. Effect of selective lymph node dissection based on patterns of lobe-specific lymph node metastases on patient outcome in patients with resectable non-small cell lung cancer: a large-scale retrospective cohort study applying a propensity score. J Thorac Cardiovasc Surg 2010;139:1001–6.

[9] Watanabe S, Asamura H. Lymph node dissection for lung cancer: significance, strategy, and technique. J Thorac Oncol 2009;4:652–7.

[10] Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P, Members of IASLC Staging Committee. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol 2009;4:568–77.

[11] Sobin L, Gospodarowicz M, Wittekind C. TNM Classification of Malignant Tumours. 7th edn. Oxford: Wiley-Blackwell 2009.

[12] Suzuki K, Koike T, Asakawa T, Kusumoto M, Asamura H, Nagai K *et al.*, Japan Lung Cancer Surgical Study Group (JCOG LCSSG). A prospective

radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). J Thorac Oncol 2011;6:751–6.

[13] Goldstraw P. Report on the international workshop on intrathoracic staging. London, October 1996. Lung Cancer 1997;18:107–11.

[14] Suzuki K, Kusumoto M, Watanabe S, Tsuchiya R, Asamura H. Radiologic classification of small adenocarcinoma of the lung: radiologic-pathologic correlation and its prognostic impact. Ann Thorac Surg 2006; 81:413–9.

[15] Darling GE, Allen MS, Decker PA, Ballman K, Malthaner RA, Inculet RI et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg 2011;141:662–70.

[16] Izbicki JR, Passlick B, Pantel K, Pichlmeier U, Hosch SB, Karg O et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. Ann Surg 1998;227:138–44.

[17] Wu Y, Huang ZF, Wang SY, Yang XN, Ou W. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. Lung Cancer 2002;36:1–6.

[18] Takizawa T, Terashima M, Koike T, Akamatsu H, Kurita Y, Yokoyama A. Mediastinal lymph node metastasis in patients with clinical stage I peripheral non-small-cell lung cancer. J Thorac Cardiovasc Surg 1997;113: 248–52.

[19] Prenzel KL, Mönig SP, Sinning JM, Baldus SE, Gutschow CA, Grass G et al. Role of skip metastasis to mediastinal lymph nodes in non-small cell lung cancer. J Surg Oncol 2003;82:256–60.

[20] Misthos P, Sepsas E, Athanassiadi K, Kakaris S, Skottis I. Skip metastases: analysis of their clinical significance and prognosis in the IIIA stage of non-small cell lung cancer. Eur J Cardiothorac Surg 2004;25:502–8.

[21] Watanabe S, Suzuki K, Asamura H. Superior and basal segment lung cancers in the lower lobe have different lymph node metastatic pathways and prognosis. Ann Thorac Surg 2008;85:1026–31.

[22] Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589–97.

[23] Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552–9.

[24] Satoh Y, Okumura S, Nakagawa K, Horiike A, Ohyanagi F, Nishio M et al. Postoperative ischemic change in bronchial stumps after primary lung cancer resection. Eur J Cardiothorac Surg 2006;30:172–6.

EDITORIAL COMMENT

Leave no lymph nodes behind!

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Systematic nodal dissection (SND) was defined in 1996 in an international and multidisciplinary consensus meeting sponsored by the International Association for the Study of Lung Cancer (IASLC) [1]. At that time, two standards were accepted for clinical practice: the ideal, that is, the *en bloc* removal of all the mediastinal fatty tissue and nodes followed by hilar and intrapulmonary nodal dissection; and the alternative, the removal of at least three mediastinal nodes, always including the subcarinal nodal station, and three hilar and intrapulmonary nodes. This alternative was intended for those who were not used to intraoperative nodal staging as an initial step that would lead them to the ideal standard. Nine years later, the Staging Committee of the IASLC proposed definitions for complete, incomplete and uncertain resections in lung cancer surgery [2]. By that time, clinical studies had provided consistent information on lymphatic spread, depending on the lobar location of the primary tumour [3, 4]. These studies allowed the refinement of the alternative to SND, assigning specific mediastinal nodal stations to be explored depending on the lobar location of the primary tumour. This lobe-specific SND (L-SND) was accepted to qualify a lung resection as complete,

provided there was no evidence of residual tumour, because, at least in the context of multicentre studies, survival after a less-thorough nodal dissection was not affected compared with that associated with SND [5]. This has been confirmed by the results of a recent trial, showing that there are no significant differences in long-term survival between those patients with clinical T1 and T2 N0 or non-hilar N1 tumours undergoing a thorough lymph node sampling and those undergoing complete mediastinal dissection, although this may not apply to more advanced disease [6].

The article by Maniwa *et al.* [7] published in this issue reports the results on survival and recurrence in patients with clinical and intraoperative N0 non-small-cell lung cancer who had undergone lobectomy and either SND or L-SND. The authors had two reasons to indicate L-SND: patient-related factors, such as age and co-morbidity, and tumour-related ones, such as part-solid tumours with a small area of consolidation resulting in a consolidation/tumour ratio of <0.5. After a median follow-up of 60 months, in the latter group, there were no recurrences, and overall 5-year and disease-free survival were 100%. When the remaining two groups of patients who underwent SND and

L-SND were compared, the former were significantly younger and had better lung function tests, but were otherwise similar. Their postoperative complication rates were similar, as were their 5-year overall and disease-free survival rates, and overall recurrence rate. The only statistically significant differences were the shorter operative time (a mean difference of 29 min) and the higher recurrence rate at mediastinal nodes for L-SND. There are several issues that are worth mentioning.

First, Maniwa *et al.* have shown that the complication rates associated with SND and L-SND were similar, but we do not know if the complication rate would have been worse if those patients with associated comorbidity had undergone SND. The only significant benefit of L-SND was a shorter operative time, but one wonders if a mean reduction of less than half an hour brings any real benefit to these patients. Therefore, the indication to perform L-SND based on comorbidity is questionable. Others have proved that complete mediastinal dissection and systematic sampling have similar complication and mortality rates [8].

Secondly, although overall, disease-free survival and overall recurrence rates of SND and L-SND are similar, the initial mediastinal nodal recurrence is significantly higher in L-SND. These recurrences imply new tests, cause anxiety and disappointment to patients thought to have undergone a presumed complete resection and require additional therapy. This has to be balanced against the scarce potential benefit of L-SND. When performing L-SND, some nodes are removed and others are not, based on mere statistics, and statistics are useless for the individual patient. The fact is that one is never sure of the nodal status until the pathologist studies the nodes, and to do so they must be removed. It is clear from this study that more involved nodes remained in the mediastinum when L-SND was performed, and that the intraoperative assessment, either by macroscopic assessment or by frozen sections, failed in 45 (15%)—25 pN1 and 20 pN2—of 304 patients who were thought to have clinical and intraoperative N0 diseases. It also failed to identify multinodal disease in 3 of the 4 patients with only mediastinal nodal recurrence.

Thirdly, lobectomy was the resection of choice for those patients with part-solid lesions, a consolidation/tumour ratio <0.5, low uptake on positron emission tomography and low carcinoembryonic antigen. Although the tendency today is to perform sublobar resections for these preinvasive or minimally invasive tumours, local recurrences have been reported after sublobar resections for these early tumours when the follow-up is extended beyond 5 years [9]. The results from this study also show that, for this selected group of tumours, L-SND is an adequate intraoperative nodal assessment: there were no cases with mediastinal nodal involvement, recurrence or death from cancer. Although the tumours in this subgroup seem to be early adenocarcinomas, it would have been important to specify their histological types according to their proposed revised classification [10].

And fourthly, even if some of our surgical manoeuvres do not alter the survival curves of patient cohorts, this does not mean that they do not affect the individual patients. We treat individual patients, not cohorts, and we should offer the best care to our patients. The 4% increase in N2 rate found after complete mediastinal lymphadenectomy following systematic sampling did not alter the survival curves of both groups in the ASOCOG Z0030 trial, but must have helped in making decisions on postoperative treatment and to refine the postoperative prognosis of those individual patients [6]. In the study by Maniwa *et al.*, SND might have prevented mediastinal recurrence (or, more precisely, mediastinal progression of disease left in unremoved mediastinal lymph nodes).

Maniwa *et al.* are to be commended for bringing this issue to our attention. They are cautious in their conclusion, which is more a one-sentence summary of their results than a proper conclusion. What I have learnt after reading and reflecting on their experience is that it is better for our patients if nodes are not left behind.

REFERENCES

[1] Goldstraw P. Report on the international workshop on intrathoracic staging, London, October 1996. Lung Cancer 1997;18:107–11.

[2] Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definitions. Lung Cancer 2005;49:25–33.

[3] Naruke T, Tsuchiya R, Kondo H, Nakayama H, Asamura H. Lymph node sampling in lung cancer: how should it be done? Eur J Cardiothorac Surg 1999;16(Suppl 1):17–24.

[4] Ichinose Y, Kato H, Koike H, Tsuchiya R, Fujisawa T, Shimizu N *et al.* Japanese Clinical Oncology Group. Completely resected stage IIIA non-small cell lung cancer: the significance of primary tumor location and N2 stations. J Thorac Cardiovasc Surg 2001;122:803–8.

[5] Rami-Porta R, Mateu-Navarro M, Freixinet J, de la Torre M, Torres-García AJPun YW *et al.* on behalf of the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). Type of resection and prognosis in lung cancer. Experience of a multicentre study. Eur J Cardiothorac Surg 2005;28:622–8.

[6] Darling GE, Allen MS, Decker PA, Ballman K, Malthaner RA, Inculet RI Jr *et al.* Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 trial. J Thorac Cardiovasc Surg 2011;141:662–70.

[7] Maniwa T, Okumura T, Isaka M, Nakagawa K, Ohde Y, Kondo H. Recurrence of mediastinal node cancer after lobe-specific systematic nodal dissection for non-small cell lung cancer. Eur J Cardiothorac Surg 2013;44:e59–64.

[8] Allen MS, Darling GE, Pechet TT, Mitchell JD, Herndon JE II, Landreneau RJ *et al.* ACOSOG Z0030 Study Group. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomised, prospective ACOSOG Z0030 trial. Ann Thorac Surg 2006;81:1013–20.

[9] Nakao M, Yoshida J, Goto K, Ishii G, Kawase A, Aokage K *et al.* Long-term outcomes of 50 cases of limited resection trial for pulmonary ground-glass opacity nodules. J Thorac Oncol 2012;7:1563–6.

[10] Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y *et al.* International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244–85.

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