ORIGINAL

Effect of mediastinal lymph nodes sampling in patients with clinical stage I non-small cell lung cancer

Hiromitsu Takizawa[1], Kazuya Kondo[1], Hisashi Matsuoka[1], Koh Uyama[1], Hiroaki Toba[1], Koichiro Kenzaki[1], Shoji Sakiyama[1], Akira Tangoku[1], Kazumasa Miura[2], Kiyoshi Yoshizawa[2], and Junji Morita[2]

[1]*Department of Oncological and Regenerative Surgery, Institute of Health Biosciences, The University of Tokushima Graduate School, Kuramotocho, Tokushima, Japan,* [2]*Department of Thoracic Surgery, Takamatsu Red Cross Hospital, Takamatsu, Kagawa, Japan*

Abstract : *Objective* : Systematic nodal dissection has been recommended for patients with resectable non-small cell lung cancer because of its staging accuracy. However, in patients with clinical stage I non-small cell lung cancer whether systematic nodal dissection provides more benefits than mediastinal lymph node sampling or not is controversial. In this retrospective study, we evaluated the effect of mediastinal lymph node sampling in patients with clinical stage I NSCLC. *Methods* : One hundred and nineteen consecutive patients with clinical stage I NSCLC, who underwent curative operation between January 1994 and December 2000, were retrospectively reviewed (dissection group = 58 : sampling group= 61). Systematic nodal dissection was defined as complete removal of mediastinal lymph node, and mediastinal lymph node sampling was defined as removal of lymph node levels 3, 4, and 7 for right-sided tumors and levels 5, 6, and 7 for left-sided tumors. *Results* : The total number of removed mediastinal lymph nodes in patients who underwent systematic nodal dissection was 22.1 ± 9.7, which was significantly higher than that in patients who underwent mediastinal lymph node sampling of 11.4 ± 7.0 ($p < 0.001$). Postoperatively N2 disease was detected in 8 patients (13.8%) in the dissection group and 7 (11.5%) in the sampling group. After the median follow up of 79 months, the cancer specific survival rate at 5 year was 78.0% in the dissection group and 76.2% in the sampling group ($p = 0.60$). *Conclusions* : Mediastinal lymph node sampling showed the similar effect to systematic nodal dissection in patients with clinical stage I non-small cell lung cancer. J. Med. Invest. 55 : 37-43, February, 2008

Keywords **:** *lung cancer surgery, mediastinal lymph node, prognosis*

INTRODUCTION

Lung cancer is the leading cause of death due to malignant disease in the developed world. Despite advances in variety of therapies, surgery is still the best treatment option for patients with localized non-small cell lung cancer (NSCLC) (1). For the removal of the primary tumor, a surgical procedure such as lobectomy, bilobectomy, and pneumonectomy should be selected for the purpose of complete resection. Although the role of segmentectomy is being reconsidered for NSCLC of 2 cm or less (2), lobectomy is still considered the procedure of choice for patients even with peripheral T1N0

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Address correspondence and reprint requests to Kazuya Kondo, Department of Oncological and Regenerative Surgery, Institute of Health Biosciences, The University of Tokushima Graduate School, Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-633-7144.

NSCLC (3). For the removal of mediastinal lymph nodes, many investigators insist on the importance of systematic nodal dissection (SND) for accurate staging (4-10).

To decide the adequate therapy for patients with resectable NSCLC, a more accurate preoperative evaluation is essential. Accuracy of CT in preoperative mediastinal lymph node staging was 45 to 79% (11-15). Recently, cervical mediastinoscopy or positron emission tomography (PET) scanning with 2- (fluorine-18) fluoro-2-deoxy-D-glucose (FDG) proved more accurate than computed tomography (CT) in demonstration and staging of nodal involvement (11-13). However, advancements in CT have been allowing us to detect more detailed information and CT is still widely used for assessment of mediastinal involvement.

To clarify whether the effect of lymph node sampling (LS) is equal to that of SND or not, we compared the effect of LS with SND in patients with clinical stage I (cT1 or cT2, and cN0) NSCLC.

MATERIALS AND METHODS

Patients

One hundred and nineteen consecutive patients with clinical stage I NSCLC, who underwent curative operation between January 1994 and December 2000 at Tokushima University Hospital and Takamatsu Red Cross Hospital, were retrospectively reviewed (SND = 58 : LS = 61). In this period, patients with clinical stage I NSCLC underwent principally lobectomy with SND at Tokushima University Hospital and with LS at Takamatsu Red Cross Hospital. These hospitals are related institutions, therefore the criteria of preoperative examinations and diagnosis are the same. Patients were preoperatively assessed by chest x-ray, chest and upper abdomen CT scan, brain MRI, and bone scintigraphy. Patients were included into the study if they presented no lymph node swelling in hilar and mediastinal lymph nodes, and no evidence of distant metastasis. Hilar and mediastinal lymph nodes more than 1cm in short-axis diameter according to the CT scan were regarded as metastatic lymph nodes. Patients with previous or coexistent malignant disease were excluded from the study. None of the patients in the study received preoperative chemotherapy or radiotherapy. Patients who underwent SND at Tokushima University Hospital were included in the SND group, and patients who underwent LS at Takamatsu Red Cross Hospital were included in the LS group.

Surgical Procedures

For patients with SND, surgical approach was via posterolateral thoracotomy in the fifth intercostal space. For the patients with LS, surgical approach was via small lateral thoracotomy in the fifth intercostal space with the use of thoracoscopy. The technique of resection of the primary lung cancer was the same in both groups. Patients who underwent segmentectomy or partial resection were excluded from the study.

In the LS group, the resection was combined with a regional lymph node dissection of interlobular, peribronchial, and hilar nodes representing nodes 10, 11, and 12 according to the lymph node mapping proposed by Naruke, *et al* (16). A mediastinotomy was performed via longitudinal incision of the mediastinal pleura, and nodes of regions 2 to 9 were explored. Any nodes showing evidence of cancer were removed and submitted for pathohistologic analysis. However, no patient underwent perioperative pathohistologic examination and converted from LS to SND perioperatively. For right-sided tumors, nodes of regions 3, 4, and 7, and for left-sided tumors, nodes of regions 5, 6, and 7 were removed routinely in all patients. Patients who underwent inadequate lymph node sampling were excluded from the study.

In the SND group, resection was combined with a radical systematic *en bloc* mediastinal lymph node dissection as described by Naruke (17) and Martini (18). Briefly, in right-sided tumors, the superior mediastinal compartment, contained between the trachea, the superior vena cava from the level of the azygos vein to the right subclavian artery, and the right recurrent laryngeal nerve, was dissected and the trachea, azygos vein, superior vena cava, and ascending aorta were completely freed from all tissue. The azygos vein and the vagus nerve were generally spared, and the right laryngeal nerve was exposed. The anterior mediastinum anteriorly to the superior vena cava was also routinely removed, including the associated thymic tissue. Subcarinal, paraesophageal, and inferior pulmonary lymph nodes were removed *en bloc*. For sampling reasons, contralateral hilar nodes were also excised. In left-sided cancers, the subaortic compartment, contained between the left pulmonary artery, the aortic arch, the left recurrent laryngeal, and the phrenic nerve, was dissected by completely freeing the left vagal nerve and the recurrent laryngeal nerve. Thereafter, the

aortopulmonary ligament of Botalli was ligated and divided and the aortic arch was mobilized anteriorly to facilitate dissection of paratracheal nodes (nodes 3 and 4). Lymph node dissection in the inferior mediastinum was performed similarly to that on the right side. Routinely, contralateral hilar nodes were removed for sampling.

Postoperative evaluations

The number of mediastinal lymph nodes was counted according to the pathologic reports. Patients who postoperatively proved to have N2 disease underwent cis-diamminedichloroplatinum-based adjuvant chemotherapy. Patients who did not leave the hospitals after surgery or died from causes other than the original NSCLC were excluded. Patient follow up data were obtained by direct patient contact at each hospital, or by replies to prognosis investigation mail. The follow-up data were obtained through to May 2004.

Statistical Methods

Comparisons between patient characteristics were made by Pearson's chi square test. The numbers of removed lymph nodes are expressed as mean and means ± standard deviations. The student t test was used to compare the number of removed lymph nodes. The end point of this study was overall cancer specific survival, which was calculated from the date of operation to that of death. Survival probability was calculated by the Kaplan-Meier method. The log-rank test was used to compare survivals between groups. A p value of less than 0.05 was considered to be significant.

RESULTS

Patient characteristics

Patient characteristics are listed in Table 1. There was no significant difference in age, gender, histologic type, clinical T stage, tumor location, and surgical procedure between the two groups. All patients were treated by lobectomy or pneumonectomy. The SND group included 2 bilobectomies and 2 sleeve lobectomies, and the LS group included 2 bilobectomies and 1 pneumonectomy.

Table 1. Patient characteristics

		SND (n = 58)		LS (n = 61)		p Value
Age	<70yr	38	(65.5%)	39	(63.9%)	0.86
	≧ 70yr	20	(34.5%)	22	(36.1%)	
Gender	Male	39	(67.2%)	32	(52.6%)	0.10
	Female	19	(32.8%)	29	(47.4%)	
Histologic type	Adenocarcinoma	44	(75.9%)	46	(75.4%)	1.00
	Squamous cell ca.	12	(20.7%)	13	(21.3%)	
	Others	2	(3.4%)	2	(3.3%)	
Clinical T stage	cT1	42	(72.4%)	38	(62.3%)	0.24
	cT2	16	(27.6%)	23	(37.7%)	
Tumor location	Right	38	(65.5%)	39	(63.9%)	0.86
	Left	20	(34.5%)	22	(36.1%)	
Surgical procedure	Lobectomy	56	(96.6%)	58	(95.1%)	0.62
	Bilobectomy	2	(3.4%)	2	(3.3%)	
	Pneumonectomy	0	(0%)	1	(1.6%)	

SND = systematic nodal dissection ; LS = lymph node sampling

The number of removed mediastinal lymph nodes

We demonstrated the mean number of removed lymph nodes at each station in Table 2. The total number of removed mediastinal lymph nodes in patients who underwent SND was 22.1 ± 9.7, which was significantly higher than that in patients who underwent LS of 11.4 ± 7.0 ($p < 0.001$). And the number of mediastinal lymph nodes on both sides was significantly higher in the SND group than in the LS group.

Table 2. Number of removed mediastinal lymph nodes

Station No.	SND (n = 58)		LS (n = 61)		p Value
	Right (n = 38)	Left (n = 20)	Right (n = 39)	Left (n = 22)	
1	2.2	0.1	0.3		
2					
3				0.4	
3a	14.9*	3.8	8.3*		
3p					
4		3.8**		0.3	
5				4.5	
6		1.5		0.9	
7	7.1	5.3	4.4	1.7	
8	0.6	0.4	0.1	0.4	
9	0.6	1.3	0.05	0.4	
	25.4 ± 8.8		13.2 ± 7.8		$p < 0.001$
total	16.2 ± 8.9		8.4 ± 4.3		$p < 0.001$
	22.1 ± 9.7		11.4 ± 7.0		$p < 0.001$

Station numbers are classified according to Naruke's numbering system (19)
Values are presented as means and means ± standard deviations.
"*including 2, 3, 3a, 3 p, and 4. **including 4 and 5."
SND = systematic nodal dissection ; LS = lymph node sampling

Cancer specific survivals between the SND and the LS

The median follow up time was 82 months in the SND group, and 77 months in the LS group. The cancer specific survival rate in the 119 patients at 5 years was 77.2%, and the 5-year survival rate in patients with pN0, pN1, and pN2 was 83.4%, 69.2%, and 46.7%, respectively. The Kaplan-Meier survival curves of the SND and the LS groups are depicted in Figure 1, and 5-year survival rate was 78.0% in the SND group and 76.2% in the LS group. There was no significant difference between the two groups ($p = 0.60$). Figure 2 and 3 show the survival curves of clinical T1 and T2 cases, respectively. The survival rate in patients with cT1 who underwent SND and LS at 5 year was 84.8% and 81.1%, respectively. And, the survival rate in patients with cT2 who underwent SND and LS at 5 year was 58.9% and 67.5%, respectively. There was no significant difference in survival of both T1 and T2 cases between the SND and the LS groups.

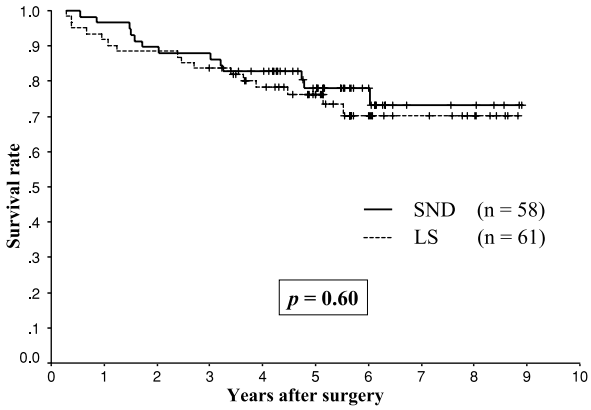

Figure 1. Survival curves of patients treated with systematic nodal dissection (SND) and lymph node sampling (LS).

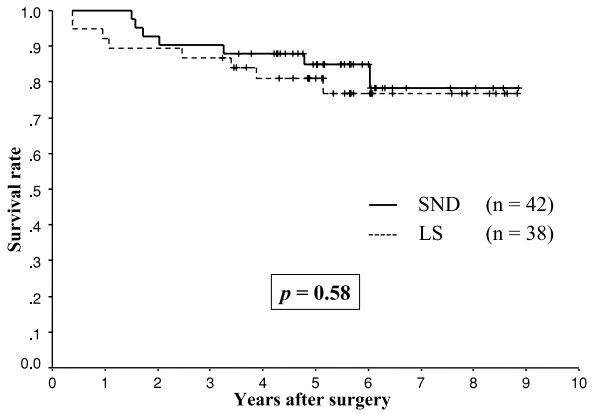

Figure 2. Survival curves of clinical T1 patients treated with systematic nodal dissection (SND) and lymph node sampling (LS).

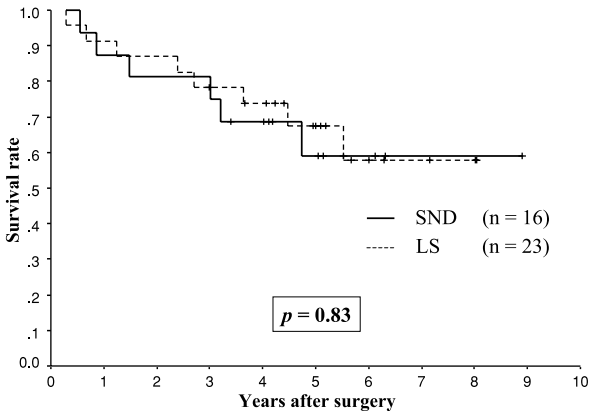

Figure 3. Survival curves of clinical T2 patients treated with systematic nodal dissection (SND) and lymph node sampling (LS).

N stage migration

The number of patients who postoperatively proved to be N1 was 5 (8.6%) in the SND group and 8 (13.1%) in the LS group. The number of patients who proved to be N2 was 8 (13.8%) in the SND group and 7 (11.5%) in the LS group. There was no significant difference in these proportions between the SND and the LS groups (Table 3). There was no patient with N3 disease. There were 5 patients with single-level N2 disease in the SND group and 4 patients with that in the LS group.

Table. 3 N stage migration

	SND (n = 58)		LS (n = 61)		*p* value
pN0	45	(77.6%)	46	(75.4%)	
pN1	5	(8.6%)	8	(13.1%)	0.71
pN2	8	(13.8%)	7	(11.5%)	

SND = systematic nodal dissection ;
LS = lymph node sampling

Survivals of subgroups of patients with different pathological N stages

There was no significant difference in pN0 cases between the SND group and the LS group, and the 5-year survival rate was 80.1% in the SND and 86.2% in the LS group (Figure 4). For a small group of pN1 and pN2 cases, though the 5-year survival rate of 69.2% for patients who underwent SND was relatively better than 5-year survival rate of 45.0% for patients who underwent LS, there was also no significant difference between two groups (p = 0.27, Figure 5).

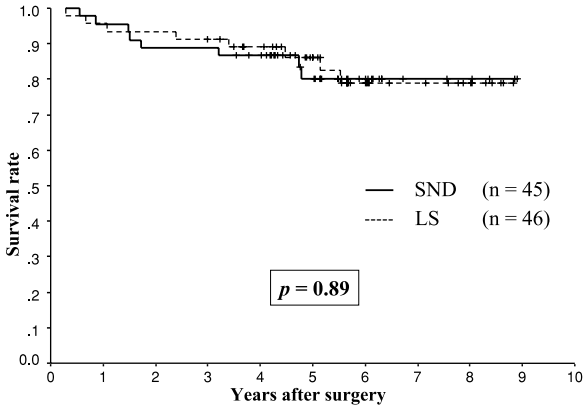

Figure 4. Survival curves of pathologic N0 patients treated systematic nodal dissection (SND) and lymph node sampling (LS).

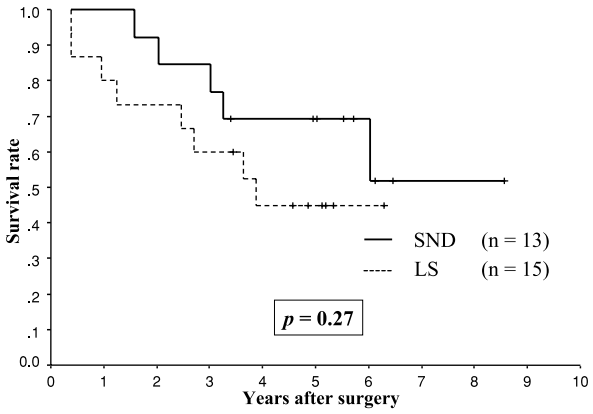

Figure 5. Survival curves of pathologic N1 and N2 patients treated with systematic nodal dissection (SND) and lymph node sampling (LS).

DISCUSSION

Many investigators have emphasized the importance of SND for patients with resectable NSCLC, because its staging accuracy can contribute to patient selection for adjuvant therapy and prediction of prognosis (4-10). However, there have been a limited number of randomized prospective trials that had compared SND with LS in patients with NSCLC (4, 5, 19). Izbicki (4) and Wu (5) investigated patients with a wide range of clinical stages which included clinical stage I to IIIA, while Sugi (19) investigated a rather limited population which included patients with peripheral lung cancer smaller than 2 cm in diameter. Therefore, the benefit of SND for the patients with clinical stage I NSCLC is still controversial.

In the present study, we found no significant difference in cancer specific survival between SND and LS in patients with clinical stage I NSCLC. Sugi and colleagues (19) reported that there was no significant difference in recurrence rate or survival in patients with NSCLC smaller than 2 cm in diameter between SND and LS. Izbicki and colleagues (4) also found that SND did not influence disease-free or overall survival in patients with clinical N0 or N1, and M0 NSCLC compared to LS. These studies support our result. Although Wu and colleagues (5) showed SND provided a significantly better prognosis than LS in patients with pathological stage I NSCLC, they did not show the result of clinical stage I disease. Therefore, we consider that the therapeutic effect of LS is equal to that of SND in patients with clinical stage I NSCLC.

The number of removed mediastinal lymph nodes in patients who underwent SND was significantly higher than that in patients who underwent LS in

our study (22.1 ± 9.7 : 11.4 ± 7.0, $p < 0.001$). However, there was a strong similarity in the percentage of patients with pathological N1 or N2 disease in both groups (SND : LS, pN1 ; 8.6% : 13.1%, pN2 ; 13.8% : 11.5%). Izbicki (4) and Sugi (19) also demonstrated that the frequency of patients with pN1 or pN2 disease was similar between SND and LS groups. In the present study, we defined LS as routine removal of lymph node levels of 3, 4, and 7 for right-sided tumors and 4, 5, and 7 for left-sided tumors. Izbicki (4) and Sugi (19) defined the routine removal of lymph node levels of 4, 5, and 7 as LS. In patients with early stage NSCLC, cancer cells are most likely to metastasize to lymph node level 3 and/or 4 in right upper lobe tumor, 3 and/or 7 in right middle lobe tumor, 7 in right lower lobe tumor, 5 and/or 6 in left upper lobe tumor, and 7 in left lower lobe tumor (20). We considered that the staging accuracy of LS is equal to that of SND in clinical stage I NSCLC, if the proper extent of mediastinal lymph nodes were sampled during LS.

With the examination of the stage migration, survival according to the pathological stage, which may be affected by spurious downstaging caused by inadequate staging, should be reviewed. Izbicki (4) described that insufficiency in staging accuracy of LS might have affected poorer outcome of small group of patients with limited lymph node involvement (pN1 disease or single-level pN2 disease). In our study, there was no significant difference in pN0 cases between the SND group and the LS group. And for a small group of pN1 and pN2 cases, there was also no significant difference between two groups, though the 5-year survival rate of patients who underwent SND was relatively better than that of patients who underwent LS.

We are well aware of two problems in our study. One is that this is a retrospective study, and another is that this study included patients in two hospitals. However, there are personnel transactions between the hospitals and the preoperative examinations and diagnosis are extremely similar, because these hospitals are related institutions. Moreover, the scale of the hospitals is also similar, and the patients in the two groups were well matched. Therefore, any difference other than the treatment for mediastinal lymph nodes was considered to be minimal. Of course, our results do not have the same strength as a randomized prospective trial, however they provide a substantial basis for the design of future randomized, prospective clinical trials and treatment strategies.

Considering our result, a lobectomy with LS is strategically acceptable for patients with clinical stage I NSCLC. However, the patients who prove to have mediastinal lymph node involvement by perioperative histopathologic examination had better be converted from LS to SND, because it is still unclear whether SND brings some therapeutic benefits to the small group of pathological N2 patients. In the near future, SND will become unnecessary for patients with clinical stage I NSCLC with the progress of pre and perioperative examinations, which will provide more accurate staging. We found 11-14% of N2 disease in clinical stage I NSCLC, when lymph nodes less than 1cm in diameter by CT scan are regarded as node-negative. Several studies demonstrated that there are 12-17% of N2 positive patients who preoperatively diagnosed as N0 (4, 14, 15). And FDG-PET proved significantly more accurate than CT in demonstrating and staging of nodal involvement (12, 13). Recently, the technique of perioperative sentinel node mapping, which can identify nodal involvement at the first lymphatic drainage site, has been developed, and this is expected to detect metastatic lymph nodes of the mediastinum with a high accuracy rate (21, 22).

In conclusion, LS showed similar diagnostic and therapeutic effects to SND in patients with clinical stage I non-small cell lung cancer.

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