To sum up, DLT was noted in one of six patients in level 1, three of six patients in level 2, and one of three patients in level 3. The DLTs were pneumonitis in three patients, grade 4 leukopenia in one patient, and grade 3 esophagitis and grade 3 infection in one patient. Thus, the MTD was determined to be level 1.

Objective Response and Survival

All patients were included in the analyses of tumor response and survival. No CR, 12 PRs, and 3 SD were noted among the 18 patients and the overall response rate (95% confidence interval) was 67% (41–87%). The response rate in patients having squamous cell carcinoma was 100%, while that for non-squamous histology was 58%. The median progression-free survival time was 9.7 months. The median overall survival time has not yet been reached and the 1-year survival rate was 78%.

DISCUSSION

The feasible doses of anticancer agents in this study were paclitaxel 120 mg/m^2 and nedaplatin 80 mg/m^2 every 4 weeks. These figures are lower than those in a randomized phase II trial for stage III NSCLC conducted in the USA, where paclitaxel 135 mg/m^2 and cisplatin 80 mg/m^2 were administered every 3 weeks concurrently with thoracic radiotherapy (6). The occurrence of severe pneumonitis hampered the dose escalation of the anticancer agents in this study. A Japanese phase I/II study of weekly paclitaxel, nedaplatin and concurrent thoracic radiotherapy for stage III NSCLC showed that the DLT was also pneumonitis and that the response rate was 75% and progression-free survival was 5.6 months, similar to the outcome of this study (17). The reasons for the frequent pneumonitis in this study remain unknown. Paclitaxel was the most frequently used anticancer agent together with thoracic radiotherapy in patients with NSCLC outside Japan. A randomized phase II study of induction chemotherapy followed by concurrent chemoradiation therapy in patients with stage III NSCLC (CALGB study 9431) showed that grade 3–4 pneumonitis during chemoradiation was noted in 14% of patients treated with gemcitabine and cisplatin, 20% of patients treated with paclitaxel and cisplatin, and 20% of patients treated with vinorelbine and cisplatin. One patient died of pneumonitis in the vinorelbine and cisplatin arm (6). Thus, incidence of pneumonitis in patients receiving paclitaxel was reported to be the same as that for other agents in this setting. Nedaplatin was a new agent but one of the platinum that has been repeatedly shown to be safely administered with radiation (1). A case series of 24 esophageal cancer patients treated with radiation therapy (60–70 Gy) combined with Nedaplatin (80–120 mg) and 5-fluorouracil (500–1000 mg for 5 days) showed that toxicity was mainly hematological and no grade 3 or higher non-hematological toxicity was observed (18). Treatment-related pneumonitis may be more readily developed among Japanese patients, because gefitinib-induced pneumonitis is more common in Japan than in other countries (19–21). Similarly, a relatively high incidence of drug-induced pneumonitis was noted among Japanese patients in association with the use of weekly docetaxel (20) and leflunomide, a newly developed disease-modifying antirheumatic drug that exhibits anti-inflammatory, antiproliferative and immunosuppressive effects (22). Further studies are needed to define ethnic or geographic variation of treatment-related pneumonitis.

Recent dose–volume histogram studies showed that the volume–dose parameters such as the V20 and MLD were significantly associated with development of severe radiation pneumonitis (23). The V_{20} and MLD in the three patients who developed unacceptable pneumonitis in this study (15–30% and 822–1675 cGy, respectively) were not so large, and therefore, the severe pneumonitis in these patients could not be fully explained by their irradiation volume alone. Patient characteristics such as age, sex, smoking habit, location of the primary tumor and pre-existing lung diseases may be associated with the development of radiation pneumonitis, but their contribution was inconclusive (24).

Radiation pneumonitis is the most common dose-limiting complication of thoracic radiation. Its incidence varies greatly from one report to another: the incidence of grade 2 radiation pneumonitis was between 2% and 33% and that of grade 3 was between 0% and 20% (25). This inconsistency among reports can be explained by the different radiation pneumonitis scoring system and follow-up duration in each study. No scoring system for radiation pneumonitis is perfect. The distinction between grade 2 and grade 3 toxicity is highly subjective. In addition, these scoring systems do not account for intercurrent symptoms from tumor, infection and chronic lung illnesses such as chronic obstructive pulmonary diseases (25).

For future trials, it is an important strategy to reduce the lung volume receiving radiation without an increase in the local recurrence rate. Elective nodal regions with potential subclinical micrometastases (CTV3 in this study) have been included in the standard irradiation volume. The advent of three-dimensional conformal treatment techniques, however, has allowed for a more precise definition of target volume and may allow the possibility of reduced toxicity and increased radiation dose delivery by the omission of elective nodal irradiation (26). We are conducting a phase I study of high-dose thoracic three-dimensional conformal radiotherapy without elective nodal irradiation concurrently combined with cisplatin and vinorelbine in patients with inoperable stage III non-small cell lung cancer.

In conclusion, the doses of paclitaxel and nedaplatin combined with thoracic radiotherapy could not be escalated owing to severe pulmonary toxicity. We do not recommend a phase II study of this chemoradiotherapy regimen.

Acknowledgements

We thank Yuko Yabe and Mika Nagai for preparation of the manuscript. This study was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest statement

None declared.

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Jpn J Clin Oncol 2007;37(3)181–185
doi:10.1093/jjco/hym005

Concurrent Chemoradiotherapy for Limited-disease Small Cell Lung Cancer in Elderly Patients Aged 75 Years or Older

Toshio Shimizu[1,3], Ikuo Sekine[1], Minako Sumi[2], Yoshinori Ito[2], Kazuhiko Yamada[1], Hiroshi Nokihara[1], Noboru Yamamoto[1], Hideo Kunitoh[1], Yuichiro Ohe[1] and Tomohide Tamura[1]

[1]Divisions of Internal Medicine and Thoracic Oncology and [2]Radiation Oncology, National Cancer Center Hospital, Tokyo and [3]Department of Medical Oncology, Kinki University Nara Hospital, Ikoma, Nara, Japan

Received July 19, 2006; accepted November 8, 2006; published online April 10, 2007

Background: The optimal treatment for limited-disease small cell lung cancer (LD-SCLC) in patients aged 75 years or older remains unknown.
Methods: Elderly patients with LD-SCLC who were treated with chemoradiotherapy were retrospectively reviewed to evaluate their demographic characteristics and the treatment delivery, drug toxicities and antitumor efficacy.
Results: Of the 94 LD-SCLC patients treated with chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1998 and 2003, seven (7.4%) were 75 years of age or older. All of the seven patients were in good general condition, with a performance status of 0 or 1. Five and two patients were treated with early and late concurrent chemoradiotherapy, respectively. While the four cycles of chemotherapy could be completed in only four patients, the full dose of radiotherapy was completed in all of the patients. Grade 4 neutropenia and thrombocytopenia were noted in seven and three patients, respectively. Granulocyte-colony stimulating factor support was used in five patients, red blood cell transfusion was administered in two patients and platelet transfusion was administered in one patient. Grade 3 or more severe esophagitis, pneumonitis and neutropenic fever developed in one, two and three patients, respectively, and one patient died of radiation pneumonitis. Complete response was achieved in six patients and partial response in one patient. The median survival time was 24.7 months, with three disease-free survivors for more than 5 years.
Conclusion: Concurrent chemoradiotherapy promises to provide long-term benefit with acceptable toxicity for selected patients of LD-SCLC aged 75 years or older.

Key words: elderly – small cell lung cancer – chemotherapy – radiotherapy

INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 20% of all pulmonary neoplasms and 25–40% of patients with this disease are 70 years of age or older. The number of elderly patients with such disease are expected to increase with the growing geriatric population (1).

Because SCLC is highly sensitive to chemotherapy and radiotherapy, the standard treatment for limited-disease SCLC (LD-SCLC) has been a combination of platinum and etoposide with concurrently administered thoracic radiotherapy, as long as the patients are in good general condition (2, 3). Such elderly patients, however, may show decreased clearance of the anticancer agents commonly used for the treatment of SCLC, including cisplatin and etoposide, because of the decrease of the lean body mass, hepatic blood flow and renal function that are associated with aging. In addition, myelotoxicity is sometimes more severe in this population than in younger populations, because the absolute area of hematopoietic marrow decreases with age (4). Retrospective subset analyses of patients with LD-SCLC treated with concurrent chemotherapy and radiotherapy in phase III trials have shown that the percentage of patients in whom the planned number of chemotherapy cycles can be completed is usually 10% lower in patients

For reprints and all correspondence: Ikuo Sekine, Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo, 104-0045, Japan. E-mail: isekine@ncc.go.jp

70 years of age or older as compared with that in younger patients (5). One study reported that myelotoxicity was more severe in elderly patients than in younger patients (5), while another reported no such difference between the patients of the two age groups (6). The delivery of thoracic radiotherapy was not influenced by age in these patients (7). However, 78–85% of patients in these analyses were aged between 70 and 75 years old and a few were over 80 years old. Thus, the most suitable treatment options for elderly patients with LD-SCLC aged 75 years or older still remain unknown.

The objective of this retrospective analysis was to evaluate the patient characteristics and the treatment delivery, toxicity and antitumor efficacy of the administered treatments in LD-SCLC patients 75 years of age or older who were treated with chemotherapy and thoracic radiotherapy.

PATIENTS AND METHODS

We retrospectively reviewed the medical charts, chest X-rays and computed tomography (CT) scans of LD-SCLC patients aged 75 years or older. To evaluate the thoracic irradiation field, the standard initial field was defined as follows: the field including the primary tumor and involved nodes with a short axis length of 1 cm or more on CT scans with a 1.0–1.5 cm margin, and the subclinical ipsilateral hilum and bilateral mediastinal lymph node regions with a 1.0 cm margin. The supraclavicular lymph node regions were included only if there was tumor involvement of these nodes. Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0, Japanese edition (8). The objective tumor response was evaluated according to the WHO criteria issued in 1979 (9). The overall survival time was measured from day 1 of chemotherapy to the date of death as a result of any cause or the date of the last follow-up.

RESULTS

Of the 94 LD-SCLC patients treated with chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1998 and 2003, seven (7.4%) were 75 years of age or older (Table 1). During this period, we had three other patients with LD-SCLC who were aged 75 years or older. They were treated with chemotherapy alone because of complications in two patients and refusal of intensive therapy in one patient. There were five males and two females, and four patients were between 75 and 79 years of age and three patients were 80 years old or older. Three patients presented with persistent cough, while the remaining four patients complained of no symptoms and were diagnosed based on the detection of an abnormal shadow on a plain chest X-ray obtained during a mass screening or routine health examination program. All the patients were in good general condition. One patient had a history of inferior wall myocardial infarction suffered 9 years prior to this admission. However, echocardiography at this admission revealed normal heart function with an ejection fraction of 73%. One patient had stage I pulmonary emphysema with % FEV_1 predicted of 58%, but no abnormal findings on blood gas analysis. The % FEV_1 predicted in other four patients was within 98% and 116%, and was not measured in the other two patients. A median (range) PaO_2 level at the room air before treatment in the seven patients was 77.4 (66.9–87.2) Torr. A decreased creatinine clearance, 48.8 ml/min at a urine volume of 600 ml/day, was noted in one patient, while the other patients had a creatinine clearance of 78 ml/min or higher. Four and three patients had a performance status of 0 and 1, respectively, and five patients gave no history of loss of body weight. The diagnosis of small cell carcinoma was confirmed cytologically or histologically in all the patients.

The chemotherapy regimens used were cisplatin at 80 mg/m^2 on day 1 combined with etoposide at 100 mg/m^2 on days 1–3 in four patients aged between 75 and 19 years. For patients aged 80 years of older, carboplatin was dosed to a

Table 1. Patient characteristics

n	Age (yr)/ gender	Smoking history	Symptom	Weight loss (%)	Complications	Performance status	TNM stage
1	81/male	6/day × 62 yr	None	0	Type 2 DM	0	T1N2M0
2	81/female	20/day × 62 yr	None	0	OMI (inferior wall), thoracic aortic aneurysm	0	T1N1M0
3	80/female	20/day × 50 yr	Cough	11	Hypertension	1	T4N3M0
4	78/male	20/day × 46 yr	None	0	None	0	T2N2M0
5	77/male	30/day × 50 yr	Cough	7	COPD, Hypertension	1	T4N3M0
6	75/male	10/day × 55 yr	None	0	None	0	T1N2M0
7	75/male	10/day × 55 yr	Cough, Hoarseness	0	None	1	T4N2M0

COPD, Chronic obstructive pulmonary disease; OMI, old myocardial infarction; DM, diabetes mellitus.

target AUC of 5 by Calvert's formula on day 1 combined with etoposide at 80 mg/m^2 on days 1–3 in two patients and cisplatin at 25 mg/m^2 on days 1–3 combined with etoposide at 80 mg/m^2 on days 1–3 in one patient (Table 2). These regimens have been reported to be used in a JCOG phase III trial for elderly patients with extensive SCLC (10). Four cycles of chemotherapy could be completed in four patients, whereas only three cycles could be completed in two patients and only one cycle could be completed in one patient. The reason for discontinuation of the chemotherapy in these patients was prolonged myelosuppression in two patients and patient refusal for continuation of treatment in one patient. The chemotherapy dose was reduced in the subsequent cycles in four patients. The reasons for the dose reduction were grade 4 thrombocytopenia in two patients, grade 4 leukopenia in one patient and both grade 4 thrombocytopenia and leukopenia in one patient. Thoracic radiotherapy was started concurrently with the chemotherapy in five patients (early concurrent chemoradiotherapy). Treatment began with chemotherapy alone in the remaining two patients, because of a mild cytology-negative pleural effusion in one patient and too large an irradiation volume in the other patient. Two cycles of chemotherapy reduced the tumor volume successfully in both the patients and thoracic radiotherapy was then added concurrently with the third and fourth cycles of chemotherapy (late concurrent chemoradiotherapy). Thoracic radiotherapy was delivered using photon beams from a liniac or microtron accelerator with energy between 6 and 20 MV at a single dose of 2 Gy once daily up to a total dose of 50 Gy in four patients aged between 78 years or older and at a single dose of 1.5 Gy twice daily up to a total dose of 45 Gy in three patients aged between 75 and 77 years. This selection of conventional or hyperfractionated radiotherapy was determined arbitrarily. The initial irradiation field was judged as the standard in six patients and reduced in one patient. A multi-leaf collimator and conventional lead blocks were used for shaping of the irradiation field. The median irradiation area was 169 cm^2 (range, 95–278 cm^2). The projected total radiation dose was administered in all the patients, but a treatment delay of 5 days or longer was observed in three patients. The criteria of radiotherapy suspension were white blood cell count $< 1.0 \times 10^9$/L, platelet count $< 20 \times 10^9$/L, esophagitis $\geq$ grade 3, fever ≥ 38°C and performance status ≥ 3. The reason for the delay in the three patients was esophagitis, decreased platelet count and poor performance status.

The hematological toxicities observed in the patients are summarized in Table 3. Grade 4 leukopenia, neutropenia and thrombocytopenia were noted in four, seven and three patients, respectively. Granulocyte-colony stimulating factor support was used in five patients, red blood cell transfusion was administered in two patients and platelet transfusion was administered in one patient. The non-hematological toxicities included grade 3 or more severe esophagitis, pneumonitis and neutropenic fever in one, two and three patients, respectively. One patient died of radiation pneumonitis that developed 4 months after the end of radiotherapy (Case No. 6).

Of the seven patients, complete response was achieved in six patients and partial response in one patient (Table 3). However, prophylactic cranial irradiation was given in only one patient (Case No. 6). Three patients remained alive for

Table 2. Treatment and its delivery

n	Chemotherapy				Thoracic radiotherapy			
	Regimen (mg/m^2 if not specified)	Number of cycles	Dose reduction	Duration of one cycle (days)*	Timing	Total dose (Gy)/fractions	Field size	Delay (days)
1	C (AUC = 5) d1 + E (80) ds1–3	3	Yes	30	Early Co	50/25	S	4
2	P (25) ds1–3 + E (80) ds1–3	1	NA	NA	Early Co	50/25	S	7
3	C (AUC = 5) d1 + E (80) ds1–3	4	Yes	23	Late Co	50/25	S	14
4	P (80) d1 + E (100) ds1–3	4	Yes	26	Late Co	50/25	R	1
5	P (80) d1 + E (100) ds1–3	4	No	28	Early Co	45/30	S	3
6	P (80) d1 + E (100) ds1–3	4	No	27	Early Co	45/30	S	0
7	P (80) d1 + E (100) ds1–3	3	Yes	35	Early Co	45/30	S	7

*Calculated as follows: Duration of one cycle (days) = (Day 1 of the 1st cycle – Day 1 of the last cycle)/(Number of cycles – 1).
C, carboplatin; E, etoposide; NA, not applicable; P, cisplatin; Co, concurrent; S, standard; R, reduced.

Table 3. Toxicity, tumor response and survival

n	Hematological toxicity (grade by CTC-AE v3.0)				Blood transfusion	G-CSF support	Non-hematological toxicity ≥ grade 2 (grade by CTC-AE v3.0)	Tumor response	Survival time (mo)/outcome
	WBC	Neu	Hb	Plt					
1	3	4	1	4	Platelet	None	None	CR	80.3/Alive
2	3	4	1	2	None	Used	Pneumoniti (3), esophagitis (2), anorexia (2)	CR	21.3/Dead
3	4	4	3	4	RBC	Used	Neutropenic fever (3), esophagitis (3)	CR	65.6/Alive
4	4	4	2	1	None	Used	None	CR	97.4/Alive
5	3	4	2	3	None	Used	Neutropenic fever (3), esophagitis (2), anorexia (2)	CR	13.1/Dead
6	4	4	2	1	None	None	Pneumoniti (5), neutropenic fever (3)	CR	6.4/Dead
7	4	4	4	4	RBC	Used	None	PR	24.7/Dead

WBC, white blood cell count; Neu, neutrophil count; Hb, hemoglobin; Plt, platelet count; G-CSF, granulocyte- colony stimulating factor; CTC-AE, Common Terminology Criteria for Adverse Events; CR, complete response; RBC, red blood cell; PR, partial response.

more than 5 years without recurrence. The median survival of the seven patients was 24.7 months.

DISCUSSION

The antitumor effects of the treatment regimens were reasonably good, with six complete responses and one partial response and three long-term disease-free survivors in spite of discontinuation/dose reduction of chemotherapy. This is perhaps mainly attributable to the strict selection of patients in good general condition. Thus, we believe that the standard chemoradiotherapy can be applied to LD-SCLC patients aged 75 years or older as long as they are in good general condition.

The general condition of elderly patients, however, varies widely from patient to patient. Thus, in many elderly patients 75 years of age or older, it may be better to reduce the treatment intensity, although it may be difficult to establish the standard schedule applicable to all elderly patients. There are four possible ways to modify the intensity of therapy: (1) administer chemotherapy alone; (2) change the relative timing of chemotherapy and radiotherapy; (3) decrease the drug doses and number of cycles of chemotherapy, and (4) decrease the dose and intensity of thoracic radiotherapy.

Chemotherapy alone versus chemotherapy and thoracic radiotherapy for LD-SCLC were compared in many randomized trials between the 1970s and 1980s. A meta-analysis of these trials demonstrated survival benefit of radiotherapy added to chemotherapy in younger populations of patients less than 65 years of age, but the benefit is still unclear in older patients (11). Although the findings of this meta-analysis indicated that the standard treatment in elderly patients with LD-SCLC might be chemotherapy alone, the result based on the old trials using cyclophosphamide and doxorubicin-based chemotherapy cannot be applied in the current medical setting, because chemotherapy regimens, irradiation delivery equipment and staging procedures have all evolved greatly over time.

The relative timing of chemotherapy and radiotherapy greatly influences the severity of toxicity. In late concurrent chemoradiotherapy that follows induction chemotherapy, the chemotherapy dose can be adjusted to suit each patient by evaluating the toxicity of the previous chemotherapy. In addition, the irradiation volume can be reduced by modifying the radiation treatment planning in accordance with the extent of tumor shrinkage during the induction phase. In the two patients treated by this approach in this study, the dose of the platinum drug during the concurrent chemoradiotherapy phase was reduced to 66–75% of the initial dose and that of etoposide was reduced to 50–75% of the initial dose. Sequential chemoradiotherapy consists of induction chemotherapy and subsequent radiotherapy. Because the two treatment modalities are administered separately, the treatment dose in each can be optimized for the elderly in this approach. A phase III study of concurrent versus sequential chemoradiotherapy in LD-SCLC patients younger than 75 years old revealed a 5-year survival rate of 24% in the concurrent arm and a 5-year survival rate of 18% with a lower incidence of toxicity in the sequential arm (2). The sequential schedule has not yet been evaluated in LD-SCLC patients 75 years of age or older.

A recent phase III trial showed that etoposide at 80 mg/m^2 on days 1–3 combined with either carboplatin at AUC = 5 by Carvert's formula or cisplatin at 25 mg/m^2 on days 1–3 was feasible and effective in elderly patients with extensive-disease SCLC (10). These regimens may, therefore, be applied for the treatment of LD-SCLC as well. The standard number of chemotherapy cycles administered is four. In many elderly patients, however, all four cycles cannot be completed. In two phase II studies of two cycles

of chemotherapy and concurrent thoracic radiotherapy in elderly patients with LD-SCLC, 13–25% long-term survivors were noted (12,13). Thus, the optimal number of chemotherapy cycles in the elderly should be investigated in future trials.

Thoracic radiotherapy with accelerated hyperfractionation at a total dose of 45 Gy in 30 fractions, the standard schedule for LD-SCLC, was associated with grade 3–4 esophagitis in as high as 32% of the patients and grade 4 leukopenia in 44% of the patients (2,3,5). Thus, the conventional schedule at a total dose of 45–50 Gy in 25 fractions might be preferable in the elderly (3). The severity of esophagitis is also influenced by concomitant chemotherapy, the treatment schedule and the timing of thoracic radiotherapy.

In conclusion, concurrent chemoradiotherapy promises to offer long-term benefit with acceptable toxicity in selected patients of LD-SCLC aged 75 years or older. The optimal schedule and dose of chemotherapy and thoracic radiotherapy still remains to be established in this patient population.

Acknowledgment

We would like to thank Mika Nagai for her assistance in the preparation of this manuscript.

Conflict of interest statement

None declared.

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Lymph Node Dissection for Lung Cancer

Significance, Strategy, and Technique

Shun-ichi Watanabe, MD, and Hisao Asamura, MD

Abstract: Since Cahan (1960) reported the first 48 cases that successfully underwent lobectomy with regional lymph node dissection, which was called "radical lobectomy", this procedure was universally accepted and has remained a standard surgery for lung cancer. In recent decades, the intrathoracic reevaluation of disease at thoracotomy for lung cancer has evolved into a detailed and sophisticated assessment of disease extent. Central to this is an evaluation of nodal involvement at the mediastinal and hilar levels. This technique, termed "systematic nodal dissection" (SND), has been accepted by the IASLC to be an important component of intrathoracic staging. In this manuscript, the significance, recent strategy, and technique of lymph node dissection for lung cancer are described.

Key Words: Lung cancer, Lymph node dissection, Systematic nodal dissection, Pulmonary resection.

(*J Thorac Oncol.* 2009;4: 652–657)

In 1951, Cahan et al.[1] suggested that pneumonectomy with regional lymph node dissection should be a routine procedure for lung cancer. Then in 1960, Cahan reported the first 48 cases that successfully underwent lobectomy with regional lymph node dissection, which was called "radical lobectomy."[2] Since then, this procedure was universally accepted and has remained a standard surgery for lung cancer. The descriptions of mediastinal lymph node dissection in Cahan's reports were very similar to our routine lymph node dissection today.[1,2]

In recent decades, the intrathoracic reevaluation of disease at thoracotomy for lung cancer has evolved into a detailed and sophisticated assessment of disease extent. Central to this is an evaluation of nodal involvement at the mediastinal and hilar levels. This technique, now termed "systematic nodal dissection (SND)," has been accepted by the International Association for the Study of Lung Cancer (IASLC) to be an important component of intrathoracic staging.[3] The consensus for SND could unify the nomenclature and establish the minimal technical requirements for nodal dissection in lung cancer surgery. In this article, the significance, recent strategy, and technique of lymph node dissection for lung cancer are described.

Division of Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan.
Disclosure: The authors declare no conflicts of interest.
Address for correspondence: Shun-ichi Watanabe, MD, Division of Thoracic Surgery, National Cancer Center Hospital, Tsukiji 5-1-1, Tokyo 104-0045, Japan. E-mail: syuwatan@ncc.go.jp

ISSN: 1556-0864/09/0405-0652

Definition of Lymph Node Dissection

First, the definition of "lymph node dissection" should be reconfirmed. "Dissection" means to remove the tissue from adjacent organs and skeletonize the anatomic structures. Thus, "lymph node dissection" means the en block removal of all tissue that may contain cancer cells, including the lymph nodes and surrounding fatty tissue within anatomic landmarks such as the trachea, bronchus, superior vena cava, and the aorta and its branches, pulmonary vessels, and pericardium (Figures 1*A*, *B*). European Society of Thoracic Surgeons guidelines have defined that the aim of SND is to dissect and remove all mediastinal tissue containing the lymph nodes within anatomic landmarks.[4] Excision of at least three mediastinal nodal stations, including the subcarinal node, is recommended as a minimum requirement.[4] The nodes are separately labeled and histologically examined after dissection according to recommendations for processing and reporting of lymph node specimens.[5]

In addition, "sampling" means a lesser excision of certain nodal stations that seem to be representative or abnormal in preoperative evaluations or intraoperative findings (Figure 1*C*). Doddoli et al.,[6] Gajra et al.[7] and Massard et al.[8] suggested that sampling was inferior to SND in terms of proper staging. The term "systematic sampling" refers to a routine biopsy of lymph nodes at some levels of nodal station.[4,9] Keller et al.[9] and Gajra et al.[7] reported that systematic sampling was as effective as SND for accurately staging patients.

The Significance of Lymph Node Dissection

The significance of lymph node dissection can be discussed from two clinical aspects, accurate staging and survival benefit.

Accurate Staging

Surgeons have long been aware that the situation at thoracotomy is not always as predicted by preoperative investigations. Several studies have shown that the sensitivity and specificity for computed tomography (CT) in assessing mediastinal nodal involvement is on the order of 52 to 79% and 69 to 78%, respectively.[10,11] Although positron emission tomography is considered to be the most sensitive and accurate investigation for screening of lymph node involvement, with a sensitivity of 79 to 85% and specificity of 90 to 91% in a meta-analysis,[12] the assessment of nodal status by

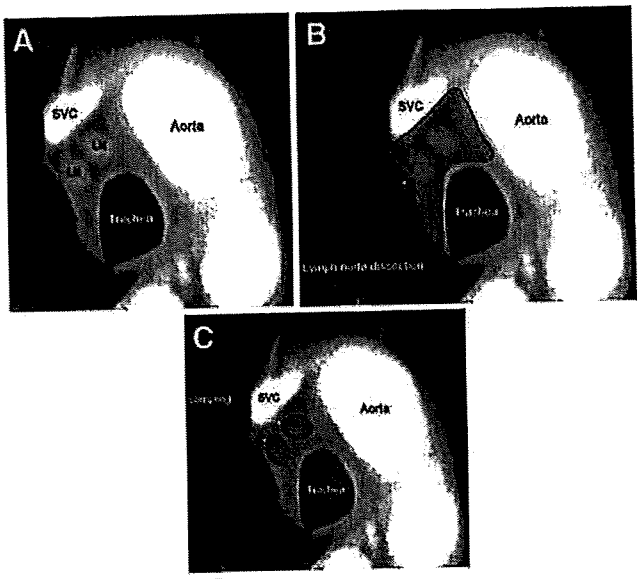

FIGURE 1. The differences in the extent of nodal dissection and sampling demonstrated on computed tomography (CT) images. *A*, Pretracheal lymph nodes and surrounding fatty tissue in the superior mediastinum. *B*, The extent of lymph node dissection. *C*, The extent of lymph node sampling. SVC, superior vena cava; LN, pretracheal lymph node.

positron emission tomography is not reliable in patients with microscopic nodal metastasis. Therefore, the intrathoracic evaluation of nodal involvement at the mediastinal and hilar levels during thoracotomy is considered to be an important component of the staging process.[13]

This technique was termed SND by the IASLC staging committee task force in 1996.[3] In the task force, the term "radical" was discarded as inferring some therapeutic benefit from this evaluation. The term "mediastinal" was also discarded because it might fail to recognize the importance of the evaluation of N1 nodes. Graham et al.[14] suggested that SND could disclose "unexpected" N2 disease irrespective of cell type, size, and location of the primary tumor, regardless of whether prior mediastinoscopy had been performed. In patients with adenocarcinomas, 60% of cN1 disease diagnosed by chest CT was histologically revealed to be N2 disease after thoracotomy.[15] Even small-sized lung cancer less than 2 cm in size shows hilar and mediastinal nodal disease with an incidence of more than 20%.[16,17] Furthermore, lung cancer has a phenomenon termed "skip metastasis" consisting of N2 disease without N1 involvement with the incidence of 20 to 38% in N2 patients.[18–22] These facts indicate the significance of SND at the mediastinal and hilar levels during thoracotomy.

Among many clinicopathological factors, the pathologic nodal status is reported to be the most significant prognostic factor.[23,24] Pathologic examination of dissected lymph nodes offers the most precise information for prognosis in patients with lung cancer. Furthermore, the recent results of some multi-institutional clinical trials evaluating the significance of adjuvant chemotherapy in patients with lung cancer showed the survival benefit of postoperative chemotherapy for node-positive patients.[25,26] Ferguson[27] reported the results of meta-analysis evaluating the cost-effectiveness of surgery for "unsuspected N2." He suggested that delaying resection until after completion of neoadjuvant therapy provided the best survival and was more cost-effective for unsuspected N2 patients. The accurate identification of positive nodes leads to selection of the optimal therapy and suggests the prognosis for each patient.[6,7]

For the aforementioned reasons, an accurate pathologic assessment for metastasis of the lymph nodes is thought to have many advantages for those with lung cancer. Therefore, SND remains an important investigative process in all patients coming to surgery for lung cancer.[28]

Survival Benefit

Others have gone further, suggesting that cure rates could be improved by lymph node dissection. Keller et al.[9] reported the comparison of survival between patients with resected stage II–IIIa non-small cell lung cancer who underwent SND and systematic sampling. This nonrandomized study showed that SND significantly improved the survival of patients with stage II–IIIa non-small cell lung cancer. Moreover, some other retrospective studies have shown the survival benefit of nodal dissection.[29–33] The survival benefit of lymph node dissection for patients with lung cancer, however, has not been statistically clear, simply because few prospective randomized controlled trials (RCTs) have been conducted comparing SND with nodal sampling (Table 1).[34–36] Izbicki et al.[34] reported no significant difference in

TABLE 1. Previous Reports of Prospective Randomized Trials Comparing Systematic Nodal Dissection and Nodal Sampling

Author	Reported Year	Years Analyzed	Detailed Description of Randomization Method	Intention-to-Treat Analysis	Patients	No. of Patients (SND/Sampling)	Median Follow-Up (Months)	Overall Survival (SND/Sampling)	Disease Free Survival
Izbicki	1998	NA	Yes	No	Operable NSCLC	169 (76/93)	47.5	HR 0.76, $p = 0.273$	HR 0.82, $p = 0.338$
Sugi	1998	1985–1992	No	No	Peripheral NSCLC less than 2 cm in size	115 (59/56)	65	5-yr survival 81.4%/ 83.9%, p = NS	NA
Wu	2002	1989–1995	No	No	Clinical stage I–IIIA NSCLC	471 (240/231)	NA	5-yr survival 48.4%/ 37.0%, $p = 0.0000$	NA

NSCLC, non-small cell lung cancer; HR, hazard ratio; SND, systematic nodal dissection; NA, not applicable.

survival between the patients with clinical stage I–IIIA lung cancer who underwent SND and nodal sampling. However, the number of enrolled patients in each arm (SND versus sampling; $n = 76$ versus 93) might have been insufficient because more than half of the subjects were node-negative patients in the pathologic examination. In a subgroup analysis, they suggested a borderline effect of SND on overall survival ($p = 0.058$) in patients with pN1 or pN2 disease.[34] Sugi et al.[35] reported no significant difference in survival between patients with peripheral cancer less than 2 cm who underwent mediastinal dissection and sampling. However, the number of enrolled patients in that study (SND versus sampling; $n = 59$ versus 56) was much less than that of the study by Izbicki. Wu et al.[36] reported the results of a prospective randomized trial with 532 patients and suggested that the SND group ($n = 268$) showed significantly better survival compared with the sampling group ($n = 264$). This study has been the only randomized study to suggest the survival benefit of nodal dissection. Wright et al.[37] reported the results of meta-analysis of these three randomized RCTs comparing SND and sampling. There was a significant reduction in the risk of death in the group undergoing SND with a hazard ratio estimated at 0.78 (95% CI 0.65–0.93; $p = 0.005$). Detterbeck[38] used the term "surprise N2" for microscopic N2 disease, and reviewed the intraoperative management of patients with "surprise N2." Based on the results of these randomized studies, he concluded that resection was justified for this subset unless it was apparent that disease would be left behind. However, the description of the randomization method in these three studies is insufficient according to the recent CONSORT statement (Table 1).[39] Collectively, whether lymph node dissection has a survival benefit is still unknown.

Who Can Attain Oncological Benefit from Lymph Node Dissection?

The most frequent relapse pattern after complete resection for lung cancer surgery is distant metastasis, even in stage I patients,[35,40] due to a distant micrometastasis that already existed at the time of surgery. Since lymph node dissection is a therapy used to achieve a better local control of cancer, this procedure does not improve the survival of the patient with distant metastasis. Moreover, in the patient who has no nodal metastasis, lymph node dissection has no impact on survival and can just prove the pathologic N0 status. Therefore, the patients who can obtain oncological benefit from nodal dissection would be those who have resectable pN2 and no distant micrometastasis, who may comprise a small group of patients with lung cancer.

Is it Possible to Conduct a Clinical Trial to Clear the Oncological Significance of Lymph Node Dissection?

Among patients with N2 disease, two types of nodal metastasis exist, the preoperatively diagnosed N2 disease (cN2-pN2) and postoperatively proven N2 disease (cN0, 1-pN2). The cN2-pN2 disease showed dismal prognosis of less than 10% of a 3-year survival after pulmonary resection.[40,41] The standard of care for cN2 disease is a chemoradiotherapy, and the role of surgery for this subset is currently unknown as described in the IASLC consensus report.[42] The patient who can attain oncological benefit from lymph node dissection should be the patient with cN0, 1-pN2 disease, i.e., "microscopic N2 disease."[43–45]

However, preoperatively recognizing and randomizing the patients with microscopic N2 is difficult because these patients can be identified mostly after completing the nodal dissection and pathologic examination.[28,46–49] Therefore, if a surgeon wants to demonstrate the oncological benefit of lymph node dissection in a RCT, extremely large numbers of patients must be enrolled in the study.

Again, thus far, the oncological benefit of lymph node dissection has not been demonstrated. To establish the survival benefit of nodal dissection in lung cancer surgery will be very difficult because of the difficulty in carrying out this sort of large RCT study and the lack of appropriate methodology. The American College of Surgery Oncology Group Z0030 study, which is a multi-institutional prospective randomized trial designed to compare the long-term survival after SND and sampling, may clear up this issue in the future.

The Concept and Technique of Lymph Node Dissection

At the time of pulmonary resection, evaluation of nodal status is performed before making any decision as to resectability.[4] As a first step, all ipsilateral hilar and mediastinal nodal stations are checked immediately after thoracotomy. The macroscopic appearance or internal architecture of the nodes is assessed by the surgeon, and if necessary, examining frozen sections of key nodes is performed. This evaluation is then repeated for the N1 nodes, extending peripherally in a centrifugal fashion until the surgeon believes that sufficient information has been gathered to decide as to the desirability of resection and the extent required.[4] This allows the surgeon to assess the feasibility and advisability of complete clearance before commencing resection.

In terms of technical aspect, SND is carried out by excising all tissue in the compartment surrounded by some anatomic structures with scissors or electrocautery. This procedure is similar to the one previously reported by Cahan in 1951.[1] As shown in Figure 2, en block removal of all tissue that may contain cancer cells, including lymph nodes and surrounding fatty tissue within anatomic landmarks, as well as the trachea, bronchus, superior vena cava, and the aorta and its branches, pulmonary vessels, and pericardium, should be performed. Special care must be taken not to interrupt the lymphatic vessels or disrupt the lymph node itself. In addition, ligating the connective tissue, which may include the small lymphatic vessels, is sometimes necessary to prevent postoperative chylothorax.

There have been reported alternative techniques for SND. Witte and Hürtgen[50] reported video-assisted mediastinoscopic lymphadenectomy technique with two-bladed spreadable videomediastinoscope. They concluded that accuracy and radicality of video-assisted mediastinoscopic lymphadenectomy could equal those of open lymphadenectomy. Zieliński[51] demonstrated transcervical extended mediastinal lymphadenectomy procedure through 5 to 8 cm collar inci-

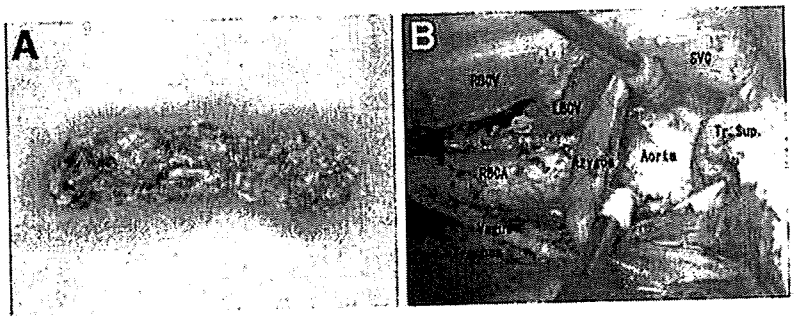

FIGURE 2. Photographs after completing systematic nodal dissection of the right superior mediastinum. *A*, Removed lymph nodes and surrounding fatty tissue en block within anatomic landmarks. *B*, Skeletonized anatomic structures after systematic nodal dissection. SVC, superior vena cava; Tr. Sup., superior trunk of the right pulmonary artery; RBCV, right brachiocephalic vein; LBCV, left brachiocephalic vein; RBCA, right brachiocephalic artery.

sion in the neck. This technique enabled complete removal of all mediastinal nodal stations except for the pulmonary ligament nodes and the most distal left paratracheal nodes. Zieliński[52] also reported the new technique of transcervical right upper lobectomy with transcervical extended mediastinal lymphadenectomy.

The Extent of Lymph Node Dissection

The extent of lymph node dissection for lung cancer has changed little since Cahan reported "radical lobectomy" in 1960.[2] SND involves the identification of nodal stations and their labeling in accordance with an internationally recognized nodal chart. Several lymph node maps have been proposed,[53,54] each with its advantages and disadvantages.[55] The one most widely used is that proposed by Naruke in 1978.[53] The Japan Lung Cancer Society published the detailed definitions of each nodal station, providing a definition for each station based on CT and surgical findings, and was intended for clinical use. The map has been used mostly in Japan because the explanatory manual only became available in English in 2000.[56]

In 1997, Mountain and Dresler[54] published the new map, which has been widely favored by the American Thoracic Society and the European Respiratory Society, among others.[57–59] This map is included in the American Joint Committee on Cancer handbook and in the Union Internationale Contre le Cancer tumor node metastasis atlas.[60] With these maps, extensive nodal dissection, including the superior and inferior mediastinum (i.e., SND), has been universally performed in lung cancer surgery.[6,7,61]

The lobe-specific patterns of nodal metastases have become recognized due to increasing analyses of the lymph node metastatic pathway. Asamura et al.[62] and Okada et al.[63] reported that right upper lobe tumors and left upper segment tumors 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.[63] suggested that lower lobe tumors seldom metastasize to the superior mediastinal nodes without concomitant metastasis to the hilar or subcarinal nodes. Considering the results of lobe-specific patterns of nodal metastases, the preoperative evaluation of the nodal status and strategy of nodal dissection has been changing, especially in stage I lung cancer (Table 2).[64–67] As the detection of early lung cancer is increasing, the extent of nodal dissection should be tailored by considering, for example, the tumor location, tumor size, cell type, and percentage of ground glass opacity area on CT scan in each tumor. This type of tailored dissection was termed "lobe-specific SND" by European Society of Thoracic Surgeons guidelines.[4] For lobe-specific SND, the "key nodes," which are easily sampled and checked during surgery by examining frozen sections, has been explored in each lobe tumor.[62–67] The definition of complete resection for lung cancer proposed by a subcommittee of IASLC staging committee includes the requirements of no residual tumor after SND or lobe-specific SND.[68]

TABLE 2. The Strategy of Selective Nodal Dissection Based on Lobe-Specific Patterns of Nodal Spread

	Location of the Primary Tumor		
Extent of Nodal Dissection	RUL LUL-Superior Segment	RML LUL-Lingular Segment	RLL LLL
Superior mediastinal nodes	Advisable	Advisable	Not always necessary[a]
Inferior mediastinal nodes			
Subcarinal node (#7)	Not always necessary[b]	Advisable	Advisable
Paraesophageal node (#8) and pulmonary ligament node (#9)	Unnecessary	Unnecessary	Advisable

[a] May be unnecessary when hilar and subcarinal (#7) nodes are negative on frozen section.
[b] May be unnecessary when hilar and superior mediastinal nodes are negative on frozen section.
RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

Summary

Although clear evidence regarding the survival benefit of lymph node dissection for lung cancer is lacking, lobectomy with lymph node dissection has been a standard surgical procedure for lung cancer. It will take more several years to obtain the final results of the ACOSOG Z0030 randomized trial to establish whether SND will improve patient survival. However, SND remains an important investigative process in staging patients and takes just within 30 minutes[40,69]; moreover, the initial results of ACOSOG Z0030 randomized trial found no increase in morbidity or mortality from lymph node dissection.[70] Thus, little benefit seems to currently exist in limiting nodal dissection.

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Gender difference in survival of resected non–small cell lung cancer: Histology-related phenomenon?

Jee Won Chang, MD,[a] Hisao Asamura, MD,[b] Riken Kawachi, MD,[b] and Shun-ichi Watanabe, MD[b]

Objective: It remains controversial whether there is a gender difference in survival of patients with resected non–small cell lung cancer.

Methods: We retrospectively analyzed 2770 patients (1689 men and 1081 women) with non–small cell lung cancer who underwent pulmonary resection between 1995 and 2005 at the National Cancer Center Hospital, Tokyo. A gender difference in survival was studied in all patients, in those divided according to histology or pathologic stage, and in propensity-matched gender pairs.

Results: There were no differences in background, such as preoperative pulmonary function, operation procedures, or operative mortality. The proportions of adenocarcinoma and pathologic stage I in women were greater than those in men (93.6% vs 61.7% and 71.4% vs 58.6%, respectively) ($P < .001$). Overall 5-year survival of women was better than that of men (81% vs 70%, $P < .001$). In adenocarcinoma, the overall 5-year survival for women was better than that for men in pathologic stage I (95% vs 87%, $P < .001$) and in pathologic stage II or higher (58% vs 51%, $P = .017$). In non-adenocarcinoma, there was no significant gender difference in survival in pathologic stage I ($P = .313$) or pathologic stage II or higher ($P = .770$). The variables such as age, smoking status, histology, and pathologic stage were used for propensity score matching, and survival analysis of propensity score-matched gender pairs did not show a significant difference ($P = .69$).

Conclusion: Women had better survival than men; however, there was no survival advantage in propensity-matched gender pairs. A gender difference in survival was observed only in the adenocarcinoma subset, suggesting pathobiology in adenocarcinoma in women might be different from that of men.

Most studies on gender-associated differences in lung cancer have found that women have several characteristics that are different from those in men, such as younger age at presentation, larger proportions of nonsmokers and early-stage diseases, and predominance of adenocarcinoma.[1-6] However, the influence of female gender on survival remains controversial because it has been insisted that gender is not a significant prognostic factor in non–small cell lung cancer (NSCLC), although gender has been associated with smoking exposure, stage, histologic subtype, and therapeutic management.[7,8]

We believe that a unique analysis with a large database may help to clarify the influence of gender on survival. The purpose of this study is to explore gender differences in clinical characteristics and survival based on a retrospective analysis of patients with NSCLC who had undergone lung resection in a single institute during an 11-year period.

From the Cheju National University Hospital, School of Medicine, Cheju National University,[a] Jeju, South Korea; and Division of Thoracic Surgery, National Cancer Center Hospital,[b] Tokyo, Japan.

Received for publication March 23, 2008; revisions received Aug 25, 2008; accepted for publication Sept 12, 2008.

Address for reprints: Hisao Asamura, MD, Division of Thoracic Surgery, National Cancer Center Hospital 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan (E-mail: hasamura@ncc.go.jp).

J Thorac Cardiovasc Surg 2009;137:807-12
0022-5223/$36.00

doi:10.1016/j.jtcvs.2008.09.026

MATERIALS AND METHODS

From January 1995 to December 2005, 2800 patients underwent lung resection for primary lung cancer at the National Cancer Center Hospital, Tokyo. Among these, 2770 patients (1689 men and 1081 women) who underwent lung resection for NSCLC were reviewed retrospectively. This study was approved by the institutional review board.

Preoperative evaluation was done by means of history and physical examination, posteroanterior and lateral chest radiographs, and blood tests, including complete blood count and serum chemistries. Computed tomography scans of the chest and upper abdomen (including the liver and adrenal glands) were checked routinely. Bone scintigraphy and brain imaging were performed in cases of suspicious symptoms. A pulmonary function test and electrocardiography were checked routinely. Quantitative pulmonary ventilation and perfusion scan were performed in patients with marginal pulmonary function. The evaluation of chronic diseases and consultation with the corresponding physicians depended on the patients' conditions.

Patients with clinical stages I and II and selected cases of stage IIIA underwent lung resection via thoracotomy. Basically, neoadjuvant preoperative therapy was not performed except for recent cases of superior sulcus tumor. Patients with N2 disease that was detected intraoperatively received postoperative adjuvant therapy. All patients were staged on the basis of the *International Union Against Cancer TNM Classification of Malignant Tumors* staging system published in 1997,[9] and tumor histology was described according to the World Health Organization classification.[10] For tumors of adenocarcinoma with a greatest dimension of 2 cm or less, Noguchi and colleagues' classification[11] was used to describe the histopathologic details. Types A and B correspond to bronchoalveolar carcinoma in the World Health Organization classification, whereas type C corresponds to adenocarcinoma with mixed subtypes, including bronchoalveolar carcinoma and invasive adenocarcinoma. Types D, E, and F correspond to invasive solid, acinar, and papillary adenocarcinoma, respectively.

Follow-up was achieved through periodic visits to the outpatient clinic until the present time or patient's death. Operative mortality was defined as death during hospitalization for lung resection or within 30 days of operation.

CIS

Abbreviation and Acronym
NSCLC = non–small cell lung cancer

The chi-square test was used to evaluate the significance of observed differences in the proportions of patients in the various outcome categories. Survival was measured from the date of operation, and the median survival was calculated and plotted according to the Kaplan–Meier method. Differences in survivals between groups were compared with the log-rank test.

For balanced assignment of the included patients to correct gender confounding in survival, propensity score matching was used. The variables such as age (continuous), smoking status (ever or never), histologic types (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or others), and pathologic stages (I, II, III, or IV) were used. These were selected on the basis of their significant difference between both genders (Table 1). A coefficient that was calculated by logistic regression analysis was multiplied to each variable, and the sum of these values were the propensity score for individual patient.[12] Gender pairs with equivalent propensity score were selected by a 1-to-1 match. All survival comparisons and analyses were performed using SigmaPlot (Systat Software Inc, San Jose, Calif).

RESULTS

Clinical Features, Histology, and Pathologic Staging

The clinical characteristics of 2770 patients are summarized in Table 1. The distribution of histologic subtypes was significantly different between the 2 genders: There was more adenocarcinoma (93.6% vs 61.7%, $P < .001$) and less squamous cell carcinoma (4.1% vs 30.3%, $P < .001$) in women. The distribution of pathologic stages showed a statistically significant gender difference in that women had a disproportionate representation in stage I disease compared with men (71.4% vs 58.6%, $P < .001$) (Table 1).

With regard to adenocarcinoma, which was the most frequent histology (n = 2054, 74.2%), there was a significant difference in pathologic features between men and women. There were more well-differentiated tumors ($P < .001$) in women but more lymphatic ($P = .011$) or vascular invasion ($P < .001$) in men (Table 2). There were 844 T1 adenocarcinomas with a greatest dimension of less than 2 cm, and information regarding Noguchi's types was available in 604 cases (71.6%). Women had more Noguchi's type A or B ($P = .000$) and less Noguchi's type D, E, or F ($P = .000$) (Figure 1).

Survival Analysis

Overall 5-year survivals for men and women were 70% and 81%, respectively (Figure 2), and there was a statistically significant gender difference in survival ($P < .001$). In adenocarcinoma, the overall 5-year survival was 84% for women (n = 1012) and 75% for men (n = 1042) ($P < .001$). However, there was no significant gender difference in survival in non-adenocarcinoma ($P = .299$) (Figure 3). When the patients were divided into subsets according to the combination of histology and pathologic stage, overall 5-year survival of women was significantly better than that of men in pathologic stage I (95% vs 87%, $P < .001$) and pathologic stage II or higher (58% vs 51%, $P = .017$) within adenocarcinoma (Figures 4, *A* and 5, *A*). On the other hand, there was no significant gender difference in survival in pathologic stage I (79% in men vs 74% in women, $P = .313$) or pathologic stage II or higher (50% in men vs 48% in women, $P = .770$) within non-adenocarcinoma (Figures 4, *B* and 5, *B*).

TABLE 1. Characteristics of patients (n = 2770) with resected non–small cell lung cancer

	Men (n = 1689)	Women (n = 1081)	*P* value
Age (y)	64.8	62.8	<.001
$FEV_{1.0}$ (%)	76.8 ± 21.6	82.5 ± 12.7	.33
Ever-smoker (%)	77.5	22	<.001
Elevated CEA level[a] (%)	28.2	21	<.001
Operative procedures			
Wedge resection + Segmentectomy	189 (11.2%)	134 (12.4%)	.877
Lobectomy	1381 (81.8%)	921 (85.2%)	.38
Pneumonectomy	119 (7.0%)	26 (2.4%)	.665
Morbidity/mortality			
Mortality	11 (0.65%)	6 (0.65%)	.392
Serious complications[b]	11 (0.7%)	5 (0.5%)	.523
Empyema with or without BPF	34 (2%)	4 (0.4%)	<.001
Histology			
Adenocarcinoma	1042 (61.7%)	1012 (93.6%)	<.001
Squamous cell carcinoma	511 (30.3%)	44 (4.1%)	<.001
Large cell carcinoma	97 (5.7%)	10 (0.9%)	<.001
Others	39 (2.3%)	15 (1.4%)	.077
Pathologic stage			
CIS	2 (0.1%)	1 (0.1%)	
p stage I	990 (58.6%)	772 (71.4%)	<.001
p stage II	320 (18.9%)	111 (10.3%)	<.001
p stage III	361 (21.4%)	190 (17.6%)	.014
p stage IV	16 (1%)	7 (0.6%)	.385

FEV, Forced expiratory volume; *CEA*, carcinoembryonic antigen; *BPF*, bronchopleural fistula; *CIS*, carcinoma in situ. [a]Preoperative CEA level > 5 ng/mL. [b]Respiratory complications that required ventilator assistance, cerebrovascular accident, congestive heart failure, or acute myocardial infarction.

TABLE 2. Pathologic features of adenocarcinoma according to gender status (n = 2054)

	Male (n = 1042)	Female (n = 1012)	*P* value
Differentiation			
Well	524 (50.3%)	678 (67%)	<.001
Moderate	345 (33.1%)	283 (28%)	.11
Poor	173 (16.6%)	51 (5%)	<.001
Lymphatic invasion			
Present	489 (46.9%)	396 (39.1%)	.011
Vascular invasion			
Present	510 (48.9%)	369 (36.5%)	<.001

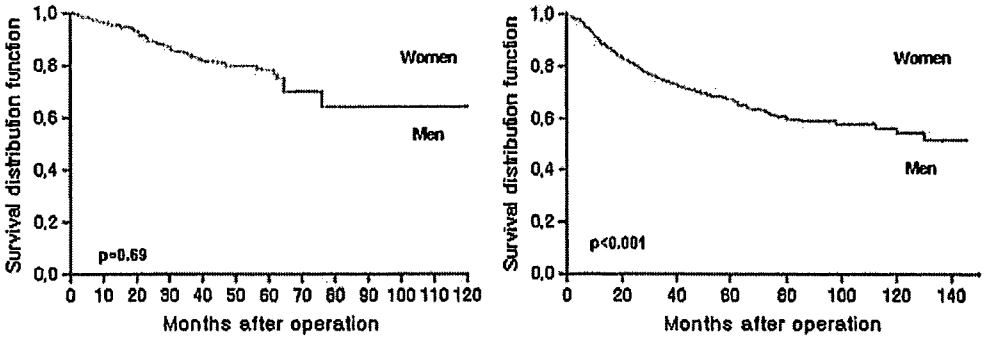

FIGURE 1. Distribution of Noguchi's type for smaller adenocarcinoma according to gender. There are significantly more Noguchi's type A or B in women and more Noguchi's type D, E, or F in men.

Propensity Score Matching

The distribution of characteristics of propensity score-matched gender pairs (n = 539) were summarized in Table 3. They were well-matched gender pairs without significant difference in clinical characteristics. There was no significant gender difference in survival in propensity score-matched gender pairs ($P = .69$) (Figure 6).

DISCUSSION

We observed a significant survival difference between men and women without notable differences in background, such as preoperative pulmonary function, type of operation procedure, or operative mortality. Although the better survival of women in the present study is consistent with several previous reports (Table 4), it can be inferred from the survival analysis of propensity score-matched gender pairs that gender is a marker of a certain risk group with different tumorigenesis rather than an independent prognostic indicator.

Several factors can be considered to be interrelated with the better survival of women: 1) histopathology; 2) internal environment, such as hormonal or genetic status; and 3) innate demographic characteristics or artifactual factors. It has been reported that the impact of tumor histology on survival is unclear. Alexiou and colleagues[13] showed that squamous cell type was an independent favorable predictor of survival, whereas others have shown no survival difference based on the cell type.[14] Women showed a significantly larger proportion of well-differentiated type adenocarcinoma (Table 2) and Noguchi's classification A or B (Figure 1). A high degree of differentiation provides a relative survival advantage,[15] and survival is significantly longer even in patients after recurrence with well-differentiated tumors than in those with moderately or poorly differentiated tumors.[16] The degree of differentiation is related to the expression of tumor suppressor gene, such as WW domain-containing oxidoreductase, and the reduced or absent expression of this gene was observed in invasive adenocarcinoma.[17] These results reflect the notion that the degree of differentiation is related to biological aggressiveness at a genetic level. It is also supported by the report that epidermal growth factor receptor mutation was correlated with subtypes of adenocarcinoma and their histologic grade.[18] On the basis of the subset analyses according to the histology and survival analysis in propensity score matching, histology is assumed to be one of the factors affecting the gender difference in survival.

The distinctive internal environment of women might be related to their better survival. It has been reported that gender-dependent differences in estrogen receptor alpha and beta expression could contribute to unique phenotypic characteristics of lung cancer in women.[19] Likewise, parathyroid hormone-related protein, which predicts longer survival in women but not in men, showed a more intense tumor suppression effect in an NSCLC model in female mice because it was regulated negatively by androgen hormone.[20] Along with hormonal influences, genes such as $p53^{R172H/+}$, $K\text{-}ras^{LA1/+}$ have been recognized to be associated with aggressive behavior and even a gender difference in cancer-related death.[21]

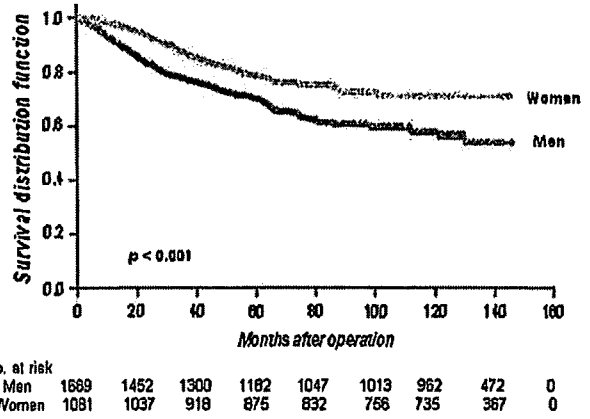

FIGURE 2. Survival curves according to gender. The overall 5-year survival is 81% for women (n = 1081) and 70% for men (n = 1689). Women show significantly better survival than men ($P < .001$).

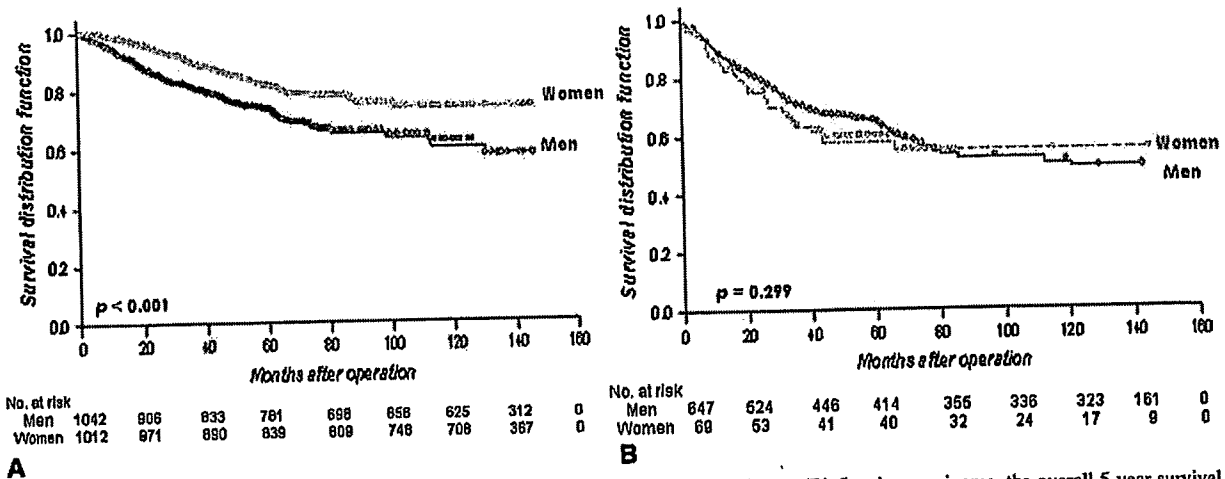

FIGURE 3. Survival curves according to gender in adenocarcinoma (A) and non-adenocarcinoma (B). In adenocarcinoma, the overall 5-year survival is 75% for men (n = 1042) and 84% for women (n = 1012). This gender difference is significant ($P < .001$). In non-adenocarcinoma, the overall 5-year survivals of men (n = 647) and women (n = 69) are 64% and 58%, respectively. This gender difference in survival is not significant ($P = .299$).

Several artifactual factors might be related to the gender difference in survival.[22] The demographics of Japan are changing so rapidly that life expectancy is increasing for women. Furthermore, a favorable mix of demographic variables, such as good performance status, more asymptomatic or screen-detected diseases, and fewer comorbidities, might affect the better survival of women, although such information was not available in this study.

One of the most remarkable results of this study is that women show better survival than men even within subsets of the same pathologic stage within adenocarcinoma, but on the other hand no difference was observed in non-adenocarcinoma subsets. One possible explanation for this result is a difference in smoking status. In contrast with non-adenocarcinoma, in most cases, adenocarcinoma in women arises in the absence of the carcinogenic effect of tobacco, or at least under the influence of only secondhand smoke from the spouse or workplace. This could be responsible for the difference in tumorigenesis and pathobiological activity of adenocarcinoma in women. In addition to this difference in smoking status, women are often exposed to different external environments, such as cooking fumes from fuels and oils, household pollutants, and industrial dust. Ko and colleagues[23] suggested that the frequency of exposure to fumes from cooking oils, when not reduced by an extractor, might be an important factor in lung cancer in nonsmoking women.

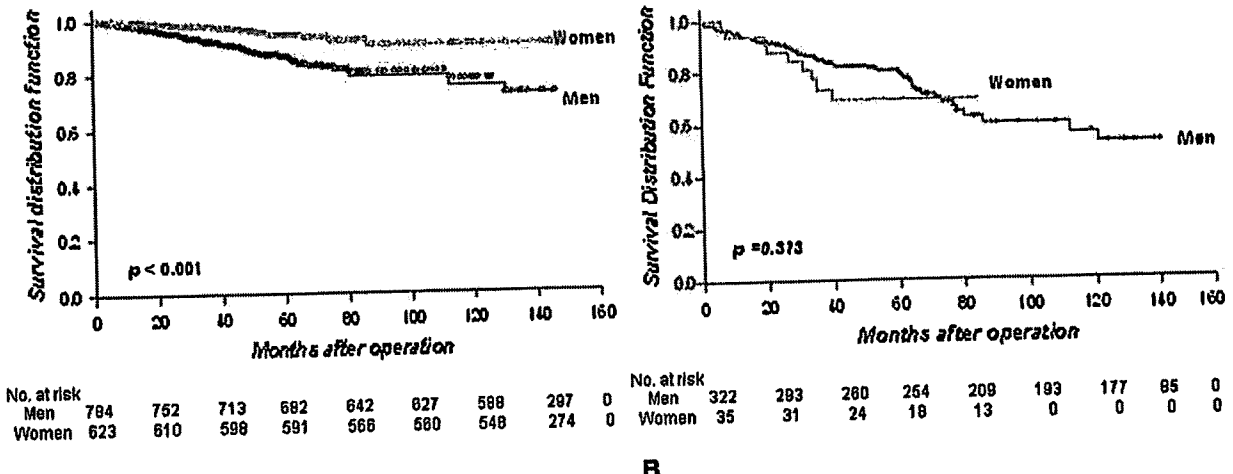

FIGURE 4. Survival curves according to gender of pathologic stage I in adenocarcinoma (A) and non-adenocarcinoma (B). The overall 5-year survival of pathologic I in adenocarcinoma for women is significantly better than that for men (95% vs 87%, $P < .001$). There is no significant gender difference in survival of pathologic stage I in non-adenocarcinoma (79% vs 74%, $P = .313$).

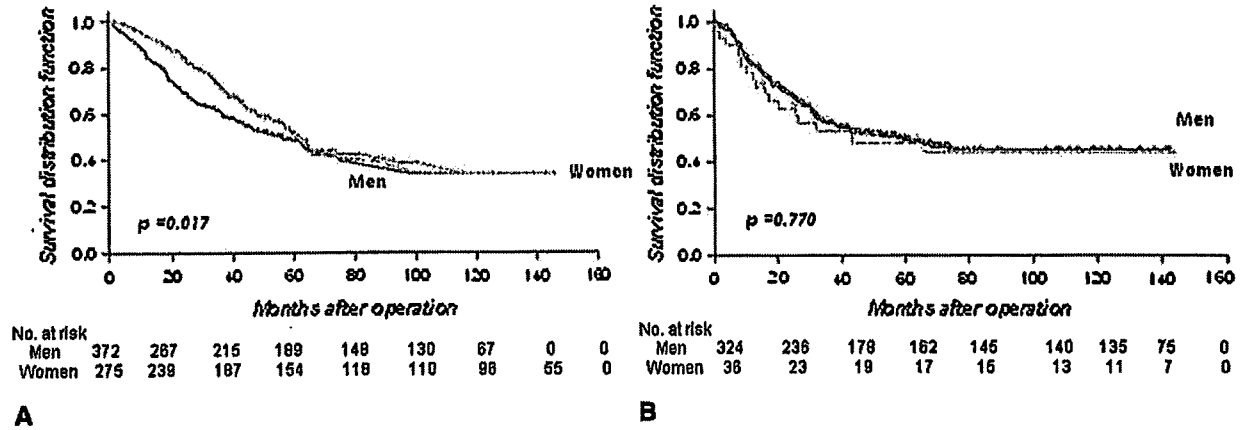

FIGURE 5. Survival curves according to gender of pathologic stage II or higher in adenocarcinoma (A) and non-adenocarcinoma (B). There is a significant gender difference in survival in the subset of adenocarcinoma (57% in women, 51% in men, $P = .017$), but not in non-adenocarcinoma (50% in men, 48% in women, $P = .770$).

TABLE 3. Characteristics of propensity-matched gender pairs (n = 1078)

	Men (n = 539)	Women (n = 539)	*P* value
Age (y)	63.4	62.8	.07
Ever-smoker	259 (48.1%)	238 (44.2%)	.22
Adenocarcinoma	448 (83.1%)	450 (83.5%)	.92
p stage I	350 (64.9%)	355 (65.9%)	.78

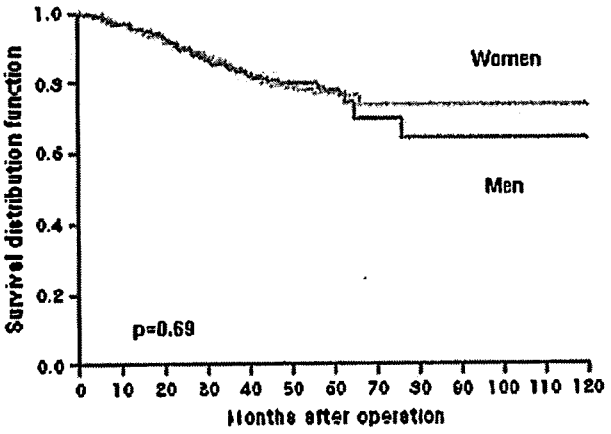

FIGURE 6. Survival curves of propensity score matched-gender pairs. There is no significant gender difference in survival ($P = .69$).

Complicated interactions in the external environment may underlie the difference in adenocarcinoma in women.

On the basis of the results regarding gender differences in the pathologic features of adenocarcinoma or survival analyses in subsets, adenocarcinoma in women is presumed to have different pathobiologic behaviors from that in men. Genetic polymorphisms, familial susceptibility, and the mutation of specific genes are now being investigated as possible causes of the biological differences in adenocarcinoma in women.[24-26] Further investigations are needed on the pathologic and biological nature of adenocarcinoma in women.

TABLE 4. Reports describing a gender difference in survival in lung cancer

Authors	Year	Years analyzed	Gender difference in survival	Comments
Ferguson and colleagues[1]	2000	1980–1998	$P = .006$	
Alexiou and colleagues[13]	2002	1990–2000	$P = .001$	Lower operative mortality in women
Cerfolio and colleagues[3]	2006	1998–2005	$P < .001$	Stages I, II, and III NSCLC
Foegle and colleagues[7]	2007	1982–1997	$P = .84$	
Asamura and colleagues[4]	2008	1999	$P = .000$	

CONCLUSIONS

There is significant gender difference in survival after resection of NSCLC. Women show significantly better overall 5-year survival than men in all patients and in subsets of adenocarcinoma within the same pathologic stage, but there was no survival advantage of women in propensity-matched gender pairs. The pathobiology in adenocarcinoma in women might be different from that in men.

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Clinicopathological Characteristics of Screen-Detected Lung Cancers

Riken Kawachi, MD, Shun-ichi Watanabe, MD, and Hisao Asamura, MD

Background: The efficacy of screening for lung cancers remains controversial, and none of the guidelines for lung cancer detection recommend screening for lung cancers. The purpose of the present study was to retrospectively analyze and characterize the clinicopathological features of screen-detected (SCR) lung cancer in comparison with lung cancers detected by other means.

Patients: The records of 2281 patients who underwent lung resection for primary lung cancer between 2000 and 2006 were analyzed retrospectively. Patients were classified into three groups according to the method of detection: SCR (n = 1290), symptom-detected (SYM, n = 481), and incidental (INC, n = 568). In the SCR group, clinicopathological factors were analyzed according to the detection modality: chest x-ray (n = 1136, 82.6%), computed tomography (CT, n = 196, 13.9%), positron emission tomography (n = 22, 1.6%), and sputum cytology (n = 17, 1.3%).

Results: The percentages of smaller (≤2 cm) lung cancer (42.6%: SCR, 19.6%: SYM, 40.9%: INC), adenocarcinoma (85.8%: SCR, 58.6%: SYM, 73.1%: INC), and pathologic stage I (73.0%: SCR, 47.0%: SYM, 71.2%: INC) were higher in the SCR group than in the other two groups. The 5-year survival rates in SCR, SYM, and INC group were 79.6%, 74.6%, and 64.6%, respectively. The patients with CT-detected lung cancer had a higher incidence of smaller size (≤2 cm, 76.4%), adenocarcinoma (92.6%), and stage I (clinical: 97.2%, pathologic: 93.1%). The 5-year survival rates in the chest x-ray and CT groups were 77.8% and 91.2%, respectively.

Conclusions: SCR lung cancers were characteristically less advanced, had a smaller diameter, and were more frequently adenocarcinoma histologically. CT-screening may be able to detect early stage lung cancers, and improve the prognosis of lung cancer patients.

Key Words: Computed tomography (CT scan), Imaging (all modalities), Lung cancer, Diagnosis and staging, Positron emission tomography (PET).

(*J Thorac Oncol.* 2009;4: 615–619)

Division of Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan.

Disclosure: The authors declare no conflicts of interest.

Address correspondence to: Dr. Hisao Asamura, Division of Thoracic Surgery, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: hasamura@ncc.go.jp

ISSN: 1556-0864/09/0405-0615

Lung cancer is the most common cause of cancer death worldwide not only in Japan but also in the other developed countries. In 2005, 45,189 males and 16,874 females died of lung cancer in Japan.[1] Early detection and surgical resection could provide the best chance for cure of lung cancers. However, previous trials using chest x-ray (CXR) and sputum cytology (SC) in heavy smokers failed to show a reduction in mortality.[2–4] Recently, several studies have shown that lung cancer can be detected in a much earlier stage.[5–12] These are the most promising recent measures for early detection using computed tomography (CT).

The objective of the present study was to identify the characteristics of lung cancer detected by screening, and to clarify whether the screen-detected (SCR) group shows better survival than other groups. The objective of the study was to compare screen detected cancers to incidental (INC) or symptomatic cancers and to evaluate survival in these groups.

PATIENTS AND METHODS

Patients

From January 2000 to December 2006, 2281 patients underwent surgical resection for primary lung cancer at the National Cancer Center Hospital in Tokyo, Japan. Medical records of all patients were reviewed retrospectively. Preoperative staging routinely included CXR and chest and abdominal CT. Positron emission tomography (PET), bone scan, and brain magnetic resonance imaging were performed only when further examination was required. All patients were staged clinically and pathologically according to the International Union Against Cancer tumor node metastasis classification system.[13] The histology of the tumor was described according to the World Health Organization classification.[14] The present study focused on patients with non-small cell carcinoma (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma).

Grouping by Method of Detection

The method of detection was categorized as SCR (n = 1279, 56.1%), symptom-detected (SYM, n = 466, 20.4%), or INC (n = 536, 23.5%). The patient characteristics are shown in Table 1. In the SCR group, clinicopathological factors were further analyzed according to the detection modality: CXR in 1047 (81.9%), CT in 176 (13.8%), PET in 20 (1.6%), and SC in 17 (1.3%). The characteristics according to the detection modality are shown in Table 2. The modality was defined as the primary method used to detect the abnormality.