43 of the 44 female patients and 153 of the 160 male patients. Gefitinib was given to 7 female and 25 male patients, and erlotinib to 1 female and 1 male patient. Thus, in all, EGFR-TKIs were given to 8 (18.2%) female and 26 (16.3%) male patients.

Table 1. Patient characteristics

Characteristics	Female ($n = 44$)		Male ($n = 160$)		*P* value
	N	%	*N*	%	
Age					
Median (range)	57 (29–74)		58 (35–78)		0.28
Smoking history					
Never	24	55	5	3	<0.001
Former	5	11	77	48	
Current	15	34	78	49	
Body weight loss					
≤4.9%	36	82	126	79	0.66
≥5.0%	8	18	34	21	
Performance status					
0	12	27	51	32	0.62
1	32	73	107	67	
2	0		2	1	
Histology					
Adenocarcinoma	32	73	88	55	0.034
Non-adenocarcinoma	12	27	72	45	
Stage					
IIIA	17	39	69	43	0.53
IIIB	27	61	91	57	
Period					
1994–99	17	39	47	29	0.24
2000–05	27	61	113	71	

Table 2. Grade 3–4 toxicity

Toxicity	Grade	Female ($n = 44$)		Male ($n = 160$)		*P* value
		N	%	*N*	%	
Leukopenia	3	23	52	79	49	0.44
	4	9	21	33	21	
Neutropenia	3	13	30	49	31	0.19
	4	15	34	51	32	
Thrombocytopenia	3	1	2	5	3	0.97
	4	0		1	1	
Febrile neutropenia	3	9	21	37	23	0.59
	4	1	2	1	1	
Esophagitis	3	2	5	14	9	0.79

Response and Survival

There were 3 patients showing complete response (CR), 38 showing partial response (PR) and 2 showing stable disease (SD) among the 43 female patients evaluable for response, and 10 patients showing CR, 116 showing PR, 24 showing SD and 7 showing progressive disease among the 157 male patients evaluable for response. The response rate was higher in the female than in the male patients (93% vs. 79%, $P = 0.028$). Disease progression was noted in 36 of the 44 (82%) female patients and 131 of the 160 (82%) male patients. The median PFS did not differ significantly between the sexes: 9.2 months in the females and 9.7 months in the males ($P = 0.67$, Fig. 1). The median survival time in the female and male patients was 22.3 and 24.3 months, respectively ($P = 0.64$, Fig. 2). Survival analyses in subgroups showed the

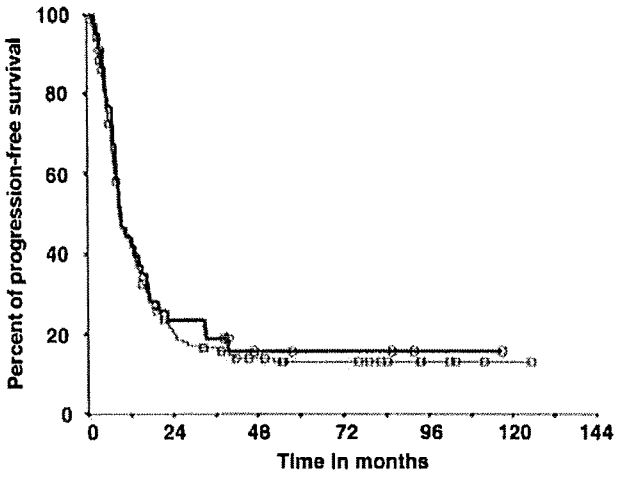

Figure 1. Progression-free survival by sex. Thick line, females; thin line, males.

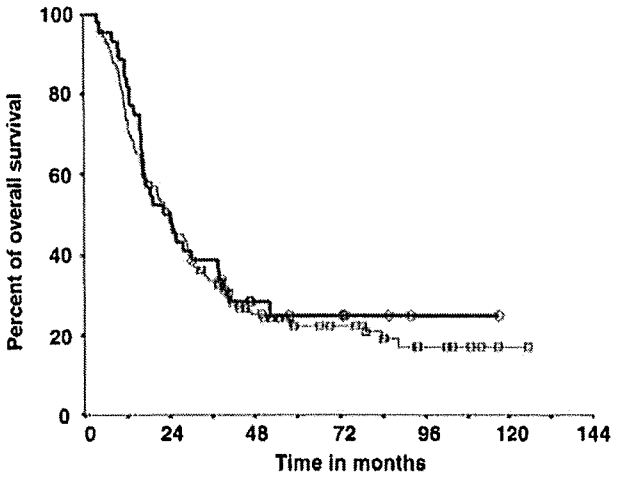

Figure 2. Overall survival by sex. Thick line, females; thin line, males.

Table 3. Factors associated with overall survival

Variables	Hazard ratio (95% confidence interval)	
	Univariate analyses	Multivariate analyses
Age	1.01 (0.99–1.03)	—
Sex		
Female	1	1
Male	1.10 (0.74–1.62)	1.16 (0.71–1.90)
Smoking habit		
No	1	1
Yes	1.00 (0.63–1.59)	0.75 (0.41–1.36)
Body weight loss		
<4.9%	1	—
≥5.0%	1.19 (0.81–1.75)	—
Performance status		
0	1	1
1–2	1.59 (1.11–2.28)	1.44 (0.97–2.15)
Histology		
Adenocarcinoma	1	1
Non-adenocarcinoma	0.76 (0.53–1.10)	0.74 (0.51–1.08)
Stage		
IIIA	1	1
IIIB	0.96 (0.70–1.32)	0.79 (0.56–1.11)
Period		
1994–99	1	1
2000–05	0.62 (0.45–0.86)	0.65 (0.45–0.92)

absence of any gender differences either among patients with adenocarcinoma or among those with non-adenocarcinoma. Similarly, no gender differences were observed either among smokers or among never-smokers. Univariate Cox's proportional hazard analyses showed that the performance status and treatment period were significantly associated with the survival (Table 3). After adjustment for the smoking history and histological type, the gender had no impact on the overall survival (Table 3).

DISCUSSION

Although prospective cohort studies and a population-based study have reported better survival in women than in men with NSCLC, these results may be biased by potential confounding factors, because these studies included highly heterogeneous patients in terms of the stage, therapy, co-morbidities and other prognostic factors (2–4). Thus, whether there is any significant difference in survival between male and female patients receiving radiation-based treatment remained controversial, and this study failed to show any significant gender difference in the survival in NSCLC patients receiving concurrent chemoradiotherapy.

Several previous studies have suggested a better prognosis in female than in male NSCLC patients treated by surgery (2,14–18), whereas our results were inconsistent with this suggestion. This may be attributable to the difference in the distribution of the disease stage (pathological stages I, II and III) between these studies and our study, including pathological stages I, II and III. The magnitude of the gender difference in survival has been suggested to vary with the disease stage. Some studies have shown a diminishing gender difference as the disease stage advanced from stages I to III, with disappearance of the gender difference among patients with stage III disease (14,15), whereas others have shown relatively constant gender difference through all the disease stages (2,16,17). A study on the gender difference in the survival in surgically resected NSCLC patients showed a better overall survival in women than men, but no significant difference in the cancer-specific survival between the two sexes (18). These results suggest that the gender difference in survival in NSCLC patients undergoing curative surgery, especially patients with early-stage disease, can be explained by the mortality related to diseases other than lung cancer.

Among local or locally advanced NSCLC patients receiving radiotherapy-based treatment, the gender difference in survival has been controversial (5–9), but potential confounding factors in these studies prevent an accurate interpretation of the results. In these studies, as high as 30% of the patients had medically inoperable stage I–II disease and 3–22% of the patients had a performance status of 2. In addition, 36–100% of patients were treated by thoracic radiation alone, whereas the others also received some form of chemotherapy as part of the treatment. Neither the current study nor another previous study showed any gender difference in the survival (10). The patients in both of these studies were limited to stage III NSCLC patients with a performance status of 0–1 who were treated by concurrent chemoradiotherapy.

Several studies have been conducted on the gender differences in survival among patients with stage IIIB–IV disease treated by systemic chemotherapy (19–24). Of these, many showed a better survival in female patients than in male patients (19–22), but the causes of this gender difference in survival remain unknown. Our previous study also showed a better survival in female patients, which was explained partly by the large number of female patients (56% vs. 44%) receiving gefitinib, and the 4-fold longer duration of gefitinib treatment (144 vs. 35 days) in these patients (25). In contrast, only 18% of the female patients and 16% of the male patients received EGFR-TKIs in this study. Thus, treatment with EGFR-TKIs had little influence on the patient survival in this study.

Clear difference in the frequency of adenocarcinoma and smoking history between female and male patients has been reported repeatedly, and this study also showed that adenocarcinoma and never-smokers were more common among the female patients. Thus, it would be reasonable to think that differences in the tumor cell characteristics between the

female and male patients may be responsible for the difference in survival between the two sexes. However, survival analyses conducted separately in subgroups among patients with adenocarcinoma and those with non-adenocarcinoma, or among smokers and non-smokers have failed to reveal any gender differences in the survival among any subgroups. In addition, a multivariate analysis showed no difference in survival between the sexes after adjustment for the tumor histology and smoking history.

The threshold for drug toxicity may also differ between women and men. In general, chemotherapy-related toxicity is reported to be slightly more severe in women, and to the best of our knowledge, there are no reports on the gender difference in radiation-related toxicity. This study showed no difference in the severity of esophagitis or hematological toxicity between the two sexes. We did not examine pulmonary toxicity in this study, because our previous large retrospective study showed no difference in the incidence or grade of pulmonary toxicity between the sexes (26).

Among several limitations of this study, the most important is the small sample size that made it difficult to draw definitive conclusions. Indeed, small difference in survival between the sexes, if any, could not be detected in this small number of patients. It is difficult, however, to expand the study population without an increase in its heterogeneity. A population-based study with >20 000 patients, for example, included patients with all stages of lung cancer, and the therapies administered were not specified. Furthermore, the quality of data on diagnosis and treatment was not uniform (4). Thus, the results of that study may be biased, despite of the huge number of patients. We cannot overlook this problem especially when analyzing stage III NSCLC patients treated with radiation-based treatment, because the quality control of radiotherapy has not been fully developed in Japan, and therefore, indication, methods and outcomes of thoracic radiotherapy may vary among hospitals.

In conclusion, this study failed to reveal any significant differences in the treatment outcomes, including survival and treatment toxicity, between female and male patients with stage III NSCLC receiving concurrent chemoradiotherapy. These results are in sharp contrast to the reported better survival in female patients with localized disease treated by surgery or those with metastatic disease treated by systemic chemotherapy.

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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.

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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.

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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

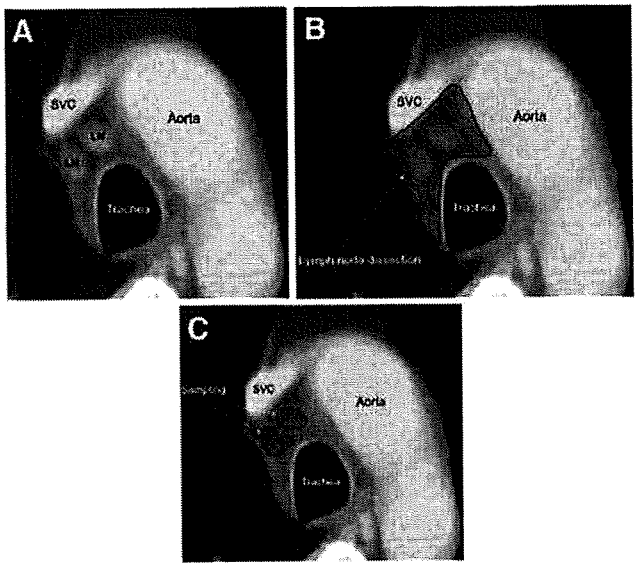

FIGURE 1. The differences in the extent of nodal dissection and sampling demonstrated on computed tomography (CT) images. *A*, Pretracheal lymph nodes and surrounding fatty tissue in the superior mediastinum. *B*, The extent of lymph node dissection. *C*, The extent of lymph node sampling. SVC, superior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

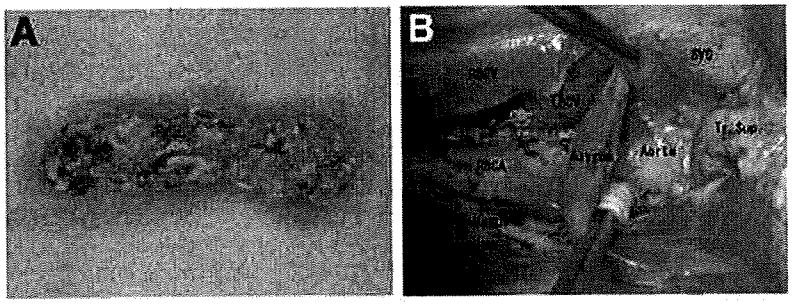

FIGURE 2. Photographs after completing systematic nodal dissection of the right superior mediastinum. *A*, Removed lymph nodes and surrounding fatty tissue en block within anatomic landmarks. *B*, Skeletonized anatomic structures after systematic nodal dissection. SVC, superior vena cava; Tr. Sup., superior 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?

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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.

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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.

GTS

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

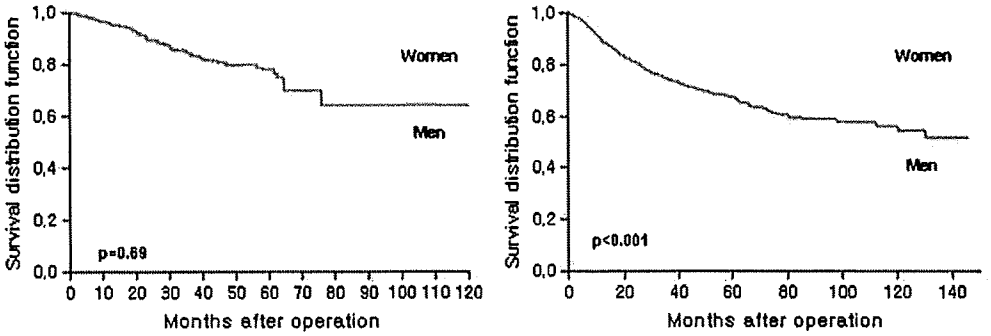

FIGURE 1. Distribution of Noguchi's type for smaller adenocarcinoma according to gender. There are significantly more Noguchi's type A or B in women and more Noguchi's type D, E, or F in men.

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 $p53^{R172H?gH+}$ $K\text{-}ras^{LA1/+}$ have been recognized to be associated with aggressive behavior and even a gender difference in cancer-related death.[21]

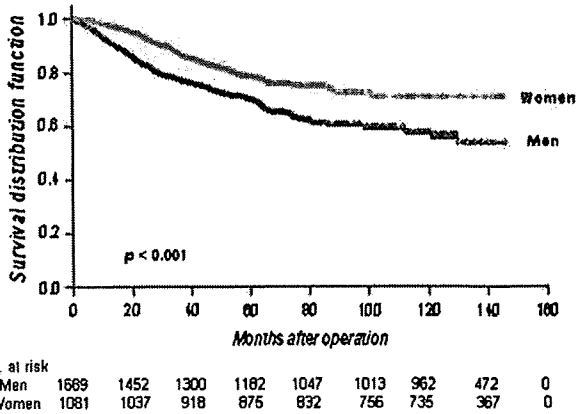

FIGURE 2. Survival curves according to gender. The overall 5-year survival is 81% for women (n = 1081) and 70% for men (n = 1689). Women show significantly better survival than men ($P < .001$).

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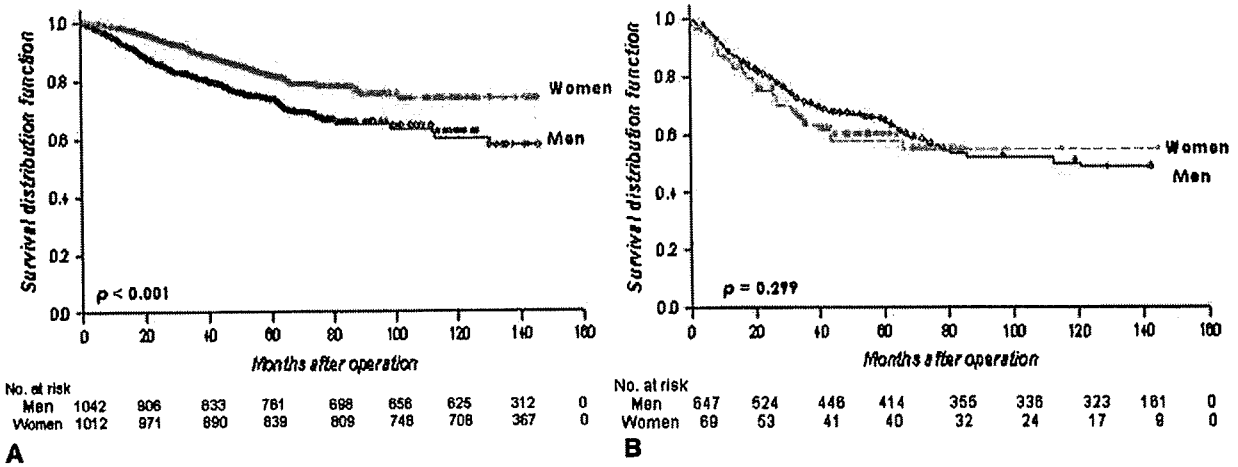

FIGURE 3. Survival curves according to gender in adenocarcinoma (A) and non-adenocarcinoma (B). In adenocarcinoma, the overall 5-year survival is 75% for men (n = 1042) and 84% for women (n = 1012). This gender difference is significant ($P < .001$). In non-adenocarcinoma, the overall 5-year survivals 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.

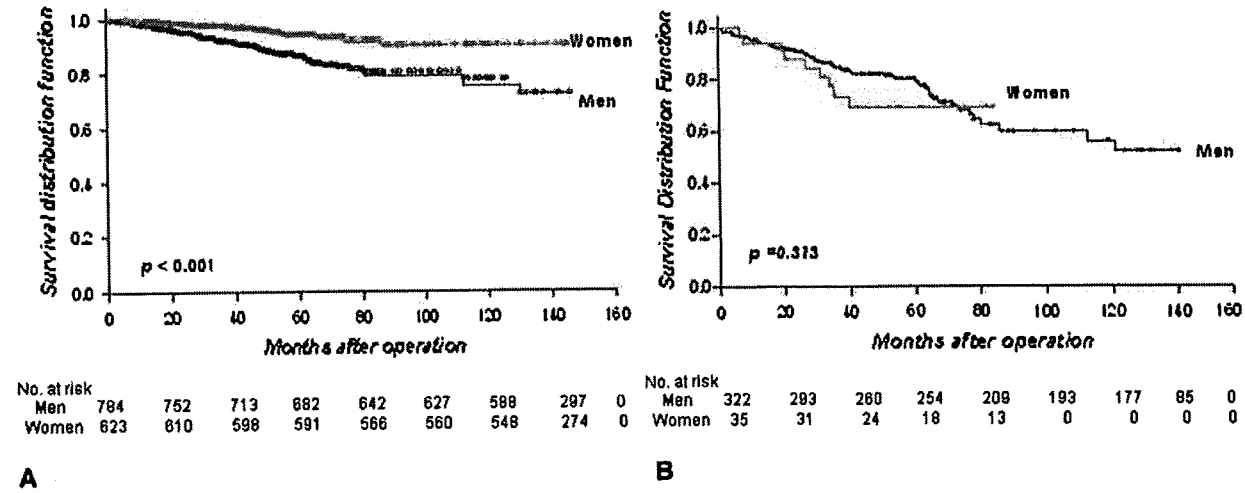

FIGURE 4. Survival curves according to gender of pathologic stage I in adenocarcinoma (A) and non-adenocarcinoma (B). The overall 5-year survival of pathologic I in adenocarcinoma for women is significantly better than that for men (95% vs 87%, $P < .001$). There is no significant gender difference in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

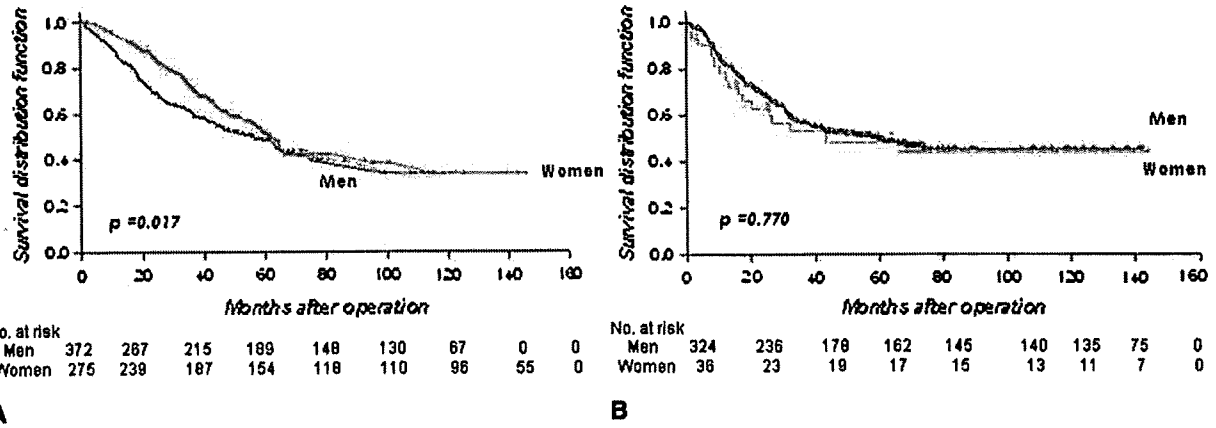

FIGURE 5. Survival curves according to gender of pathologic stage II or higher in adenocarcinoma (A) and non-adenocarcinoma (B). There is a significant gender difference in survival in the subset of adenocarcinoma (57% in women, 51% in men, $P = .017$), but not in non-adenocarcinoma (50% in men, 48%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

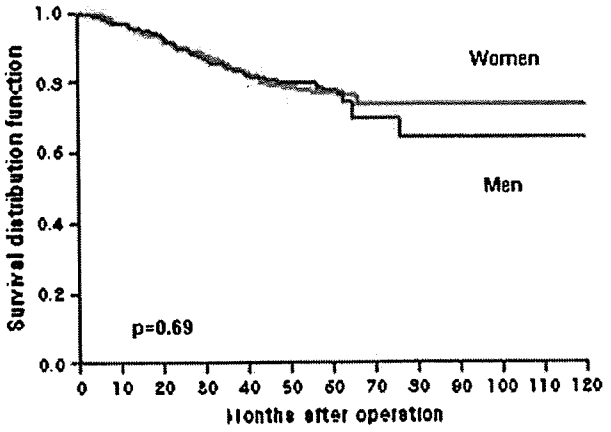

FIGURE 6. Survival curves of propensity score matched-gender pairs. There is no significant gender difference in survival ($P = .69$).

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

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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).

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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.

TABLE 1. Patient Characteristics According to the Method of Detection

Variables	Group n (%) SCR (n = 1279)	SYM (n = 466)	INC (n = 536)
Age (Median)			
Range	20–89 yr (67)	26–86 yr (65)	38–89 yr (69)
Gender			
Male	712 (55.7)	320 (68.7)	333 (62.1)
Female	567 (44.3)	146 (31.3)	203 (37.9)
Smoking histology			
Never	564 (44.2)	120 (25.9)	202 (38.1)
Ever/current	711 (55.8)	343 (74.1)	328 (61.9)
Tumor diameter			
≥2.0 cm	520 (42.6)	83 (17.8)	209 (39.0)
2.1–3.0 cm	378 (31.0)	88 (18.9)	155 (28.9)
3.1–5.0 cm	266 (21.8)	149 (32.0)	113 (21.1)
5.1–7.0 cm	44 (3.6)	74 (15.9)	25 (4.7)
>7.1 cm	12 (1.0)	29 (6.2)	9 (1.7)
Histologic type			
Adenocarcinoma	1097 (85.8)	273 (58.6)	392 (73.1)
Squamous cell carcinoma	135 (10.6)	165 (35.4)	123 (23.0)
Large cell carcinoma	39 (3.0)	17 (3.6)	17 (3.2)
Adenosquamous carcinoma	8 (0.6)	11 (2.4)	4 (0.7)
Surgical procedure			
Limited resection	132 (10.3)	25 (5.4)	80 (14.9)
Lobectomy	1066 (83.3)	366 (78.5)	428 (79.9)
Pneumonectomy	37 (2.9)	51 (10.9)	13 (2.4)
Exploratory thoracotomy	44 (3.4)	24 (5.2)	15 (2.8)
Clinical stage			
I	1135 (88.7)	266 (57.1)	478 (89.2)
II	83 (6.5)	114 (24.5)	30 (5.6)
III	58 (4.5)	78 (16.7)	26 (4.9)
IV	3 (0.2)	8 (1.7)	2 (0.4)
Pathological stage			
I	905 (70.8)	208 (44.6)	373 (69.6)
II	128 (10.0)	105 (22.6)	72 (13.4)
III	237 (18.5)	146 (31.3)	87 (16.2)
IV	9 (0.7)	7 (1.5)	4 (0.8)

SCR, screen-detected; SYM, symptom-detected; INC, incidental; T, tumor.

The type of screening was roughly divided into three groups; screening sponsored by local government, screening held by company, and screening at patients' expense. The last screening consists of members who pay dues and are entitled to screening. Furthermore, members can choose the modality of screening depending on the price. Thus, many types of screening were enrolled in this study. The SYM group was defined as patients who complained of the kind of respiratory symptom, and the incidentally detected group was defined as patients who were detected during screening for other diseases.

Statistical Analysis

Survival was calculated using the Kaplan-Meier method and differences in survival were determined by log-rank analysis. The median follow-up time for patients was 35.1 months. p values lower than 0.05 were considered statistically significant.

RESULTS

Characteristics of Screen-Detected Lung Cancer

Screen-detected lung cancers were smaller in diameter (<2 cm: 42.6%), less advanced (p-stage I: 70.8%), and showed a higher incidence of adenocarcinoma (85.8%). Incidentally detected lung cancers showed a similar tendency to SCR lung cancers, but SYM lung cancers were larger diameter, more advanced. Several characteristic findings were observed in CT-detected lung cancers: smaller diameter (<2 cm: 76.4%), less advanced (clinical stage I: 97.2%, pathologic stage I: 93.1%), and more frequently adenocarcinoma histologically (92.6%).

Survival According to the Method of Detection

The overall 5-year survival rate for the 2281 patients was 75.4%. The 5-year survival rates for the SCR, SYM, and INC groups were 79.6%, 74.6%, and 64.6%, respectively. The differences between the three groups were statistically significant (SCR versus SYM: $p < 0.0001$, SCR versus INC: $p = 0.0377$). The survival curves according to the method of detection are shown in Figure 1. Of the 2281 total patients, 1486 had pathologic stage I non-small cell lung cancer. In this subgroup, the 5-year survival rates overall and in the SCR, SYM, and INC groups were 89.6%, 92.9%, 84.0%, and 84.6%, respectively (Figure 2). The 30-day mortality was 3 patients in SCR, 5 patients in SYM, and no patients in INC group.

Survival of Screen-Detected Lung Cancer According to Modality

The 5-year survival rates for the CXR, CT, PET, and SC were 77.8%, 91.2%, 90.9%, and 80.9%, respectively. The difference in survival between the detection modalities was significant ($p = 0.0127$). Moreover, 896 patients had pathologic stage I non-small cell lung cancer, and the overall 5-year survival rates for the CXR and CT were 81.4% and 91.7%, respectively ($p < 0.0001$) (Figure 3).

Adenocarcinoma Equal to or Smaller than 2 cm in Diameter

Of 1762 adenocarcinomas, 733 had a maximal diameter of less than 2 cm. Of these, 477 were in the SCR group. Bronchioloalveolar carcinoma (BAC) was observed in 76 patients (6.1%) and invasive adenocarcinoma in 392 patients (31.5%). The distribution of the types is shown in Table 3. No patients with adenocarcinomas were observed in the SC group, and no patients with BACs were detected by PET. The proportion of BAC in the CT group (22.2%) was much higher than that in CXR (3.5%).

TABLE 2. Patient Characteristics According to the Modality of Detection in the Screen-Detected Group

Variables	Subgroup *n* (%)			
	CXR (*n* = 1047)	CT (*n* = 176)	PET (*n* = 20)	SC (*n* = 17)
Age (Median)				
Range	20–89 yr (63)	42–82 yr (63)	44–76 yr (65)	45–82 yr (65)
Gender				
Male	565 (54.0)	104 (59.1)	13 (65.0)	16 (94.1)
Female	482 (46.0)	72 (40.9)	7(35.0)	1 (5.9)
Smoking history				
Never	470 (45.0)	95 (50.0)	14 (70.0)	1 (5.9)
Ever/current	574 (55.0)	80 (50.0)	6 (30.0)	16 (94.1)
Tumor diameter				
≤2.0 cm	359 (36.2)	133 (76.4)	11 (55.0)	12 (70.6)
2.1–3.0 cm	339 (34.2)	24 (13.8)	5 (25.0)	2 (11.8)
3.1–5.0 cm	241 (24.3)	16 (9.2)	4 (20.0)	1 (5.9)
5.1–7.0 cm	40 (4.0)	1 (0.6)	0 (0)	2 (11.8)
>7.1 cm	12 (1.2)	0 (0)	0 (0)	0 (0)
Histologic type				
Adenocarcinoma	898 (85.8)	163 (92.6)	17 (85.0)	6 (35.3)
Squamous cell carcinoma	105 (10.0)	12 (6.8)	2 (10.0)	11 (64.7)
Large cell carcinoma	36 (3.4)	1 (0.6)	1 (5.0)	0 (0)
Adenosquamous carcinoma	8 (0.8)	0 (0)	0 (0)	0 (0)
Surgical procedure				
Limited resection	67 (6.4)	55 (31.3)	5 (25.0)	3 (17.7)
Lobectomy	901 (86.1)	120 (68.2)	15 (75.0)	14 (82.3)
Pneumonectomy	37 (3.5)	0 (0)	0 (0)	0 (0)
Exploratory thoracotomy	42 (4.0)	1 (0.6)	0 (0)	0 (0)
Clinical stage				
I	911 (87.0)	171 (97.2)	19 (95.0)	15 (88.2)
II	78 (7.4)	2 (1.1)	1 (5.0)	0 (0)
III	56 (5.3)	3 (1.7)	0 (0)	1 (5.9)
IV	2 (0.2)	0 (0)	0 (0)	1 (5.9)
Pathological stage				
I	705 (67.3)	163 (92.6)	16 (80.0)	12 (70.6)
II	118 (11.3)	5 (2.8)	2 (10.0)	1 (5.9)
III	216 (20.6)	8 (4.6)	2 (10.0)	3 (196)
IV	8 (0.8)	0 (0)	0 (0)	1 (5.9)

CXR, chest x-ray; CT, computed tomography; PET, positron emission tomography; SC, sputum cytology.

Type of Disease According to Smoking in Screen-Detected Lung Cancer

The relationship between smoking and type of disease is shown in Table 4. In the never-smoking-group, the incidence of noninvasive carcinoma such as bronchioloalveolar carcinoma was higher than that in patients with smoking history. As for advanced diseases, the incidence was more frequent in current or previous smokers.

Comment

The present study provides the latest data on screenings for lung cancers in patients who underwent surgical resection. SCR lung cancers were not only smaller (2 cm or less in diameter: 42.6%) and at a lower stage (stage I: 73.0%), but also more often adenocarcinoma (85.8%) than SYM lung cancers. In particular, such findings were more evident with CT in the SCR group (2 cm or less in diameter: 76.4%, pathologic stage I: 93.1%, and adenocarcinoma: 92.6%). The characteristics of SCR lung cancers in other reports were similar to those in the present study. Sobue et al.[7] reported that 82% of patients with lung cancers had stage I lung cancer. The International Early Lung Cancer Action Project (I-ELCAP) [12] also reported that the incidence of stage I lung cancer was 85.1% (412 of 484). In another report on CT screening for patients with a smoking history by Swensen et al.,[8] the incidence of clinical stage I non-small cell lung cancer was 66.7% (24 of 36) and the percentage of patients with cancer smaller than 2 cm was 91.6% (33 of 36). The high proportion of stage I in the present study is consistent with the results of several recent studies.

Previous studies have included high percentages of patients who were current or ever smokers in lung cancer

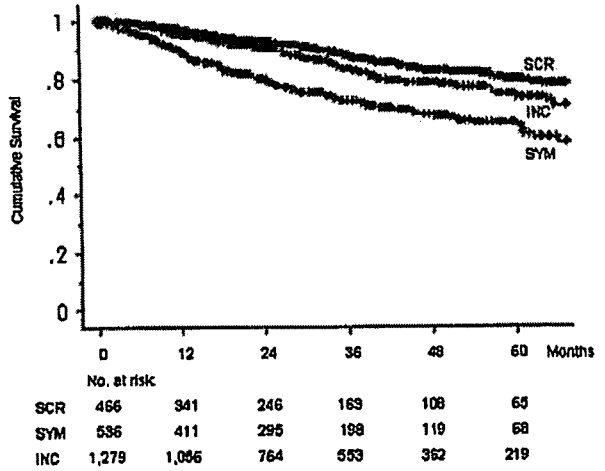

FIGURE 1. Survival curves of groups classified according to the method of detection: screen-detected, symptom-detected, and incidental group. SCR, screen-detected group; SYM, symptom-detected group; INC, incidental group.

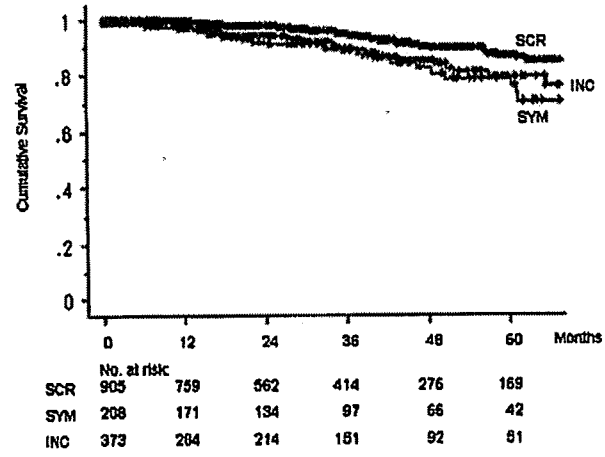

FIGURE 2. Survival curves of groups classified according to the method of detection in pathologic stage I non-small cell lung cancer. SCR, screen-detected group; SYM, symptom-detected group; INC, incidental group.

screening. The present study was not limited to such patients, and the patients had a different background. The percentage of patients with a smoking history in the SCR group was only 55%, which was lower than the rates in the other groups. In the SCR group, the incidence of squamous cell carcinoma histology was 17.7% (126 of 711) in ever or current smokers, and this value was significantly higher than that in never smokers. In the report by Swensen et al.,[8] the percentage of squamous cell carcinoma was 13.8% (4 of 29), which is similar to the result in the present study despite the presence of patients with a smoking history. However, the incidence of adenocarcinoma histology was 97.9% (552 of 564) in never smokers, and screening for all histologic types including adenocarcinoma must not be limited to smokers.

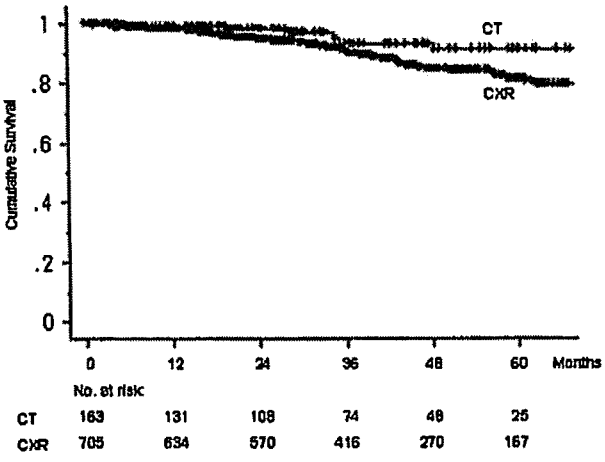

FIGURE 3. Survival curves according to the screening modality in pathologic stage I non-small cell lung cancer. CT, computed tomography; CXR, chest x-ray.

TABLE 3. Classification of Adenocarcinoma Equal to or Smaller than 2 cm in Diameter

	Subgroup *n* (%)			
Type	CXR (*n* = 1047)	CT (*n* = 176)	PET (*n* = 20)	Total (*n* = 1243)
BAC[a]	37 (3.5)	39 (22.2)	0 (0)	76 (6.1)
Invasive Ad[b]	294 (28.1)	89 (50.6)	9 (45.0)	392 (31.5)

[a] There were no patients with adenocarcinoma that was equal to or smaller than 2 cm in the diameter in sputum cytology group.

[b] Invasive adenocarcinoma includes adenocarcinoma, mixed subtype, acinar adenocarcinoma, papillary adenocarcinoma, and solid adenocarcinoma with mucin production.

CXR, chest x-ray; CT, computed tomography; PET, positron emission tomography; BAC, bronchioloalveolar carcinoma; Ad, adenocarcinoma.

TABLE 4. The Type of Disease According to Smoking History in Screen-Detected Lung Cancer

	Smoking	
Type of Disease	Never	Ever/Current
Early disease[a]	50 (65.8)	26 (34.2)
Advanced diseased[b]	100 (40.7)	146 (59.3)

[a] Noninvasive carcinoma such as Noguchi type A or B, or noninvasive squamous cell carcinoma.

[b] Pathological stage III or IV.

Another characteristic feature of the present study was a high incidence of adenocarcinoma in the SCR group (85.8%), particularly in the CT-detected subgroup (92.6%). Moreover, the incidence of BAC (≤2 cm) in CT-detected lung cancers was 22.2%, which was significantly higher than that in the CXR group (3.5%). In the I-ELCAP report,[12] BAC accounted for 7.1% of adenocarcinoma, which was a much lower incidence than that in the present study, although the present study was focused on adenocarcinoma smaller than 2cm in diameter. Lindell et al.[10] reported similar results, in