(15%). In addition, Betticher et al[19] conducted a multicenter phase 2 trial of the efficacy of neoadjuvant docetaxel-cisplatin in 90 patients with NSCLC who had locally advanced N2 disease. Using multivariate analyses, they demonstrated that mediastinal clearance (downstaging rate: 60%, $P = .0003$,) and complete resection ($P = .0006$) were strong prognostic factors. These data indicate that, in patients with stage IIIA NSCLC, downstaging in mediastinal lymph nodes significantly improves the survival outcome. Small sample size and low downstaging rate appear to be reasons why the same tendency was not observed in our patients in the CS arm. Downstaging may be related to a chemotherapy regimen and chemotherapy cycles delivered, because cisplatin is generally more effective than carboplatin in inducing tumor shrinkage, and tumor response is most efficacious at 3 cycles of chemotherapy.[20]

Induction chemotherapy or chemoradiotherapy in our present trial was well tolerated by patients in both arms, with excellent treatment compliance. No grade 3/4 fever was found in either arm, despite the high incidence of grade 3/4 neutropenia (75% in the CS arm, 89.3% in the CRS arm), nor was any grade 3/4 radiation esophagitis observed in the CRS arm. Conversely, grade 3/4 esophagitis has been recorded in 8% to 53% of patients where radiation was delivered in a hyperfractionated accelerated fashion.[9-11,17,18] More importantly, no treatment-related deaths were observed in either arm in our trial during the induction and postoperative periods. Lobectomies may be safely performed following induction therapy, whereas pneumonectomy, especially on the right, may carry an unacceptable rate of perioperative mortality.[14,15] The appropriate selection of patients to undergo resection following induction therapy is thus critical.

Our study was prematurely terminated because of poor accrual rate. We assume several reasons for poor accrual. The first reason was stage migration that upgraded former stage IIIA disease to stage IV disease due to more frequent usage of brain MRI and positron emission tomography in staging. Hence, the number of stage IIIA N2 patients is not as large as a decade ago. The second reason was the difference of definition of resectability between thoracic surgeons and pulmonary physicians (or medical oncologists). The third reason was the preference of surgeons and/or medical oncologists to treat their patients with more effective chemoradiotherapy in terms of local control. The final reason was the reluctance of some thoracic surgeons to carry out preoperative chemoradiotherapy due to the possibilities of postsurgical complications. This theme of induction therapy before surgery is extremely vital, and therefore we will have to overcome poor accrual in future randomized phase 3 trials. To accomplish the trial, it is very important to perform diagnostic procedures such as mediasitinoscopy, thoracoscopy, or bronchofiberscopic transbronchial biopsy. We also need to establish less toxic chemotherapy regimens such as carboplatin plus paclitaxel or platinum compounds plus pemetrexed, adopt less toxic radiation modality, make consensus on operability among surgeons and medical oncologists, and recruit more participating institutions.

Conclusions

The addition of radiotherapy to the induction chemotherapy regimen for stage IIIA (N2) NSCLC appears to confer better local control without adding significant adverse events. The favorable local control in this CRS arm did not translate to a significant survival difference. We consider this was due to the small sample size. Tumor downstaging after induction therapy is an important factor for improving patient survival.

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CONFLICT OF INTEREST DISCLOSURE

The authors made no disclosure.

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CHEST

Original Research

LUNG CANCER

Characteristics of Subsolid Pulmonary Nodules Showing Growth During Follow-up With CT Scanning

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Objective: **The positive results of a screening CT scan trial are likely to lead to an increase in the use of CT scanning, and, consequently, an increase in the detection of subsolid nodules. Noninvasive methods including follow-up with CT scanning, to determine which nodules require invasive diagnosis and surgical treatment, should be defined promptly.**

Methods: **Between 2000 and 2008, from our database of > 60,000 examinations with CT scanning, we identified 174 subsolid nodules, which showed a ground-glass opacity area > 20% of the nodule and measured ≤ 2 cm in diameter, in 171 patients. We investigated the clinical characteristics and CT images of the subsolid nodules in relation to changes identified during the follow-up period.**

Results: **The nodule sizes ranged from 4 mm to 20 mm at the first presentation. Nonsolid nodules numbered 98. During the follow-up period, 18 nodules showed resolution or shrinkage, and 41 showed growth of 2 mm or more in diameter. The time to 2-mm nodule-growth curves calculated by Kaplan-Meier methods indicated that the 2-year and 5-year cumulative percentages of growing nodules were 13% and 23% in patients with nonsolid nodules and 38% and 55% in patients with part-solid nodules, respectively. Multivariate analysis disclosed that a large nodule size (> 10 mm) and history of lung cancer were significant predictive factors of growth in nonsolid nodules.**

Conclusions: **An effective schedule for follow-up with CT scanning for subsolid nodules should be developed according to the type of subsolid nodule, initial nodule size, and history of lung cancer.**

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Abbreviations: AIS = adenocarcinoma in situ; GGO = ground-glass opacity; HRCT = high-resolution CT; MIA = minimally invasive adenocarcinoma

Ground-glass opacity (GGO) is a hazy increased lung opacity with the preservation of bronchial and vascular margins.[1] Subsolid nodules are localized forms of GGO, being subclassified into part-solid or nonsolid nodules based on the presence or absence of a solid area, and are usually incidentally detected on CT scanning conducted for other purposes or in CT scan screening. Subsolid nodules are important since these nodules are sometimes associated with lung neoplasms with lepidic growth.[2,3]

The National Lung Screening Trial, implemented in the United States from 2002, demonstrated a significant reduction of 20% in lung cancer mortality as a result of screening with CT scans during an interim analysis.[4] This evidence is likely to lead to an increase in the use of CT scan screening for the early detection

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of lung cancer, and, consequently, a considerable increase in the detection of subsolid nodules, as observed in the CT scan screening trials reported from Japan[5] and the United States.[2]

The subject of how to manage subsolid nodules remains controversial. Although subsolid nodules were often pathologically diagnosed as adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA),[2,5] some of them did not show any growth for a long period.[6-10] Furthermore, both subsolid nodules and AIS have been discussed in relation to overdiagnosis, which is defined as a diagnosis of lung cancer that would not lead to an individual's death because of the slow growth rate and competing age-related risks for death.[2,11-13] From these situations, we consider that the detection of growth using follow-up CT scanning is an effective method to select subsolid nodules which require surgical treatment. However, it remains unclear what the most effective follow-up interval is and how long subsolid nodules should be followed. The aim of this study was to investigate the percentage of subsolid nodules that showed size changes during follow-up, and determine their characteristics, in order to establish the most effective interval and duration for follow-up with CT scanning.

Materials and Methods

CT Scan Selection and Review

From > 60,000 CT scan examinations carried out at the Tochigi Cancer Center between January 2000 and June 2008, we extracted 1,065 cases for which descriptive terms referring to GGO were used in the reports. We reviewed all images from the cases and selected target cases according to the following criteria: subsolid nodules ≤ 2.0 cm in diameter, performance of at least one high-resolution CT (HRCT) scan and a follow-up CT scan, and a proportion of GGO > 20%. We used these criteria because we intended to investigate subsolid nodules that were followed by CT scanning. Subsolid nodules > 2 cm usually underwent immediate diagnostic procedures rather than CT scan follow-up, and nodules with at least a 20% area of GGO were thought to be obvious subsolid nodules. If a patient had multiple subsolid nodules, we focused on one representative subsolid nodule which was either the largest, or a nodule with a definite solid area. Two patients had multiple subsolid nodules analyzed because the additional subsolid nodule became the representative nodule after the resection of the first subsolid nodule. The Tochigi Cancer Center institutional review board approved this retrospective study (approval No. 23-8), and waived the requirement of patient consent.

The strategy for diagnosing subsolid nodules varied according to each physician's decision. In our institution, we prefer not to use percutaneous needle biopsy for patients with lung nodules which are estimated to have a high probability of being lung cancer and thought to be potentially curable. This concept is based on our previous research which demonstrated the risk of pleural recurrence after percutaneous needle biopsy[14] and guidelines outlined by the American College of Chest Physicians.[15] In cases of large nonsolid nodules (usually > 1.5 cm in diameter) and part-solid nodules (defined as nodules consisting of both a GGO area and a solid component), we usually recommend surgical biopsy if lung cancer is strongly suspected.

CT scans were obtained with a four-detector row (Aquilion-4; Toshiba Medical Systems) or 64-detector row (Aquilion-64; Toshiba Medical Systems) scanner. The scanning parameters for the 4-detector row scanner were as follows: rotation speed, 0.5 s; tube voltage, 120 kV; tube current, 300 mA, four rows × 1-mm channels; and a pitch of 0.75. The scanning parameters for the 64-detector row scanner were as follows: rotation speed, 0.5 s; tube voltage, 120 kV; tube current, 100-400 mA (Automatic Exposure Control); detector configuration, 64 rows × 0.5-mm channels; and a pitch of 0.828. Thin-section images were reconstructed at 1-mm thicknesses with 1-mm reconstruction intervals for the four-detector row scanner, and at 0.5-mm thicknesses with 0.5-mm reconstruction intervals for the 64-detector row scanner. The measurement method to detect minute size changes in the subsolid nodule was as follows. One HRCT image that showed the nodule with the greatest diameter was selected at baseline CT scanning. Thereafter, the same or nearest level of HRCT images at each follow-up CT scan was selected by checking the anatomic structures around the nodule (such as the bronchus and pulmonary vessels); the images were simultaneously displayed on the monitor. Then, all images were synchronized and equally magnified with scale to a sufficient size for measurement, usually as large as one-half of each window. We measured the maximal diameter of the nodule in the same direction by using software in the computer to reduce inherent variability of reimaging.[16] We viewed a size change of ≥ 2 mm or more in diameter as significant.[8] In addition, we also classified growth as significant when at least 2 mm of solid area emerged in a nonsolid nodule, or the solid area grew by ≥ 2 mm in diameter.[8] Proportions of GGO were calculated using our previously reported method.[17]

Statistical Analysis

Correlations between the type of subsolid nodule and clinicopathologic characteristics were examined using the χ^2 test and the Fisher exact test. We calculated the percentage of subsolid nodules showing growth on follow-up CT scan using the Kaplan-Meier methods. In this calculation, we only used subsolid nodules that did not show shrinkage or resolution. The time to 2 mm growth was defined from the first detection on HRCT scan until the detection of growth by 2 mm or more in diameter of subsolid nodules or the solid area, or until at least a 2 mm solid area emerged. The differences in the curves were determined using the log-rank test. Multivariate analysis of several predictive factors was performed with the Cox proportional hazards regression model. In this analysis, the age and nodule diameter were divided at the median: ≤ 60 years vs > 60 years for age, and ≤ 10 mm vs > 10 mm for nodule diameter. Statistical calculations were conducted with StatView (SAS Institute Inc).

Results

Regarding type of subsolid nodule, nonsolid nodule cases numbered 98 and part-solid nodule cases numbered 76. Patients' characteristics according to the type of subsolid nodule are shown in Table 1. Pathologic examination revealed that three patients were diagnosed with atypical adenomatous hyperplasia (AAH), 36 had AIS, 11 had MIA, and six had invasive adenocarcinoma according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society

Table 1—*Clinicopathologic Characteristics of Patients With Subsolid Nodules*

Variable	Total	Nonsolid	Part-Solid	*P* Value
Sex				
Male	71	42	29	.532
Female	103	56	47	...
Age, y				
≤60	90	56	34	.104
>60	84	42	42	...
Smoking history				
No	95	55	40	.466
Yes	56	29	27	...
Unknown	23	14	9	...
History of lung cancer				
Absent	152	85	67	.022
Present	22	13	9	...
No. of subsolid nodules				
Solitary	133	80	53	.067
Multiple	41	18	23	...
Size of nodules, mm				
4-5	7	6	1	<.001[a]
6-10	79	58	21	...
11-15	57	22	35	...
16-20	31	12	19	...
Proportion of GGO				
100% (Nonsolid)	98	98	...	...
90%-99%	40	...	40	...
50%-89%	29	...	29	...
20%-49%	7	...	7	...
Surgery				
Done	56	19	37	<.001
Not done	118	79	39	...
Type of surgery				
Lobectomy	21	2	19	<.001[b]
Segmentectomy	15	4	11	...
Wedge resection	20	13	0	...
Pathologic diagnosis				
AAH	3	3	0	.086[c]
AIS	36	12	24	...
MIA	11	4	7	...
Lepidic predominant Ad	3	0	3	...
Acinar predominant Ad	3	0	3	...
Non-neoplastic lesion	0	0	0	...

AAH = atypical adenomatous hyperplasia; Ad = adenocarcinoma; AIS = adenocarcinoma in situ; GGO = ground-glass opacity; MIA = minimally invasive adenocarcinoma.

[a]4-10 mm vs 11-20 mm.

[b]Lobectomy vs segmentectomy or wedge resection.

[c]AAH, AIS, or MIA vs lepidic or acinar predominant.

classification.[18] The diameters of the three cases of AAH on HRCT scan were 7, 8, and 9 mm, respectively. None of the resected lesions were nonneoplastic lesions. Nonsolid nodules were significantly associated with a history of lung cancer, smaller nodule size, no surgery, and limited-type surgery.

Follow-up periods ranged from 1 month to 136 months with a mean of 29 months. During the follow-up periods, 18 nodules showed shrinkage or resolution, 115 showed no change, and 41 nodules showed growth. Figure 1 shows an example of a nonsolid nodule exhibiting shrinkage during a short period and an example of a nonsolid nodule showing growth. The observed growth ranged from 2 mm to 14 mm, with a mean of 4 mm. Figure 2 shows changes in the diameter of nodules and solid area for all cases that were judged to be growth. Among the 41 cases that were judged to show growth, an increase in the diameter of nodules was observed in 37 cases, an increase in the diameter of the solid area in 16 nodules, and the emergence of a solid area in nine cases, including 21 cases that showed growth for both the diameter of the nodule and solid area. Among the growth cases, four cases showed only an increase or emergence of the solid area without an increase in the nodule diameter (case 1 and 15 to 17 in Fig 2). All resected subsolid nodules that showed growth were malignant tumors with only one exception of an AAH case in which the GGO nodule showed the emergence of a solid area without increase in the nodule diameter (case 1 in Fig 2).

Figure 3 is the time to 2-mm growth curve according to the type of subsolid nodule calculated using the Kaplan-Meier method among patients who did not show shrinkage or resolution during the follow-up period. The 2-year and 5-year cumulative percentages of growing nodules were calculated as 13% and 23% for nonsolid nodules, and 38% and 55% for part-solid nodules, respectively. Figures 4 and 5 are the time to 2 mm growth curves according to the size of the nodules in patients with nonsolid (Fig 4) and part-solid (Fig 5) nodules. Larger nodules were associated with growth in both nonsolid and part-solid nodules. The results of univariate and multivariate

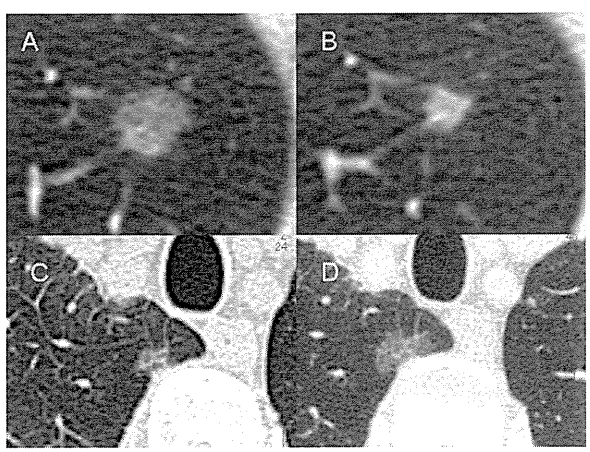

FIGURE 1. A-B, A nonsolid nodule showing shrinkage in a short period. C-D, A nonsolid nodule showing growth. Interval size changes between follow-up CT scans were measured using the same or nearest level of high-resolution CT (HRCT) image that was determined by synchronizing the anatomic structure around the nodule. A, Nonsolid nodule in the left upper lobe, measuring 10 mm in diameter at the first HRCT scan. B, After 3 mo, this nodule showed shrinkage to a polygonal shape. C, Nonsolid nodule in the left upper lobe, with a history of lung cancer. D, After 3 y and 5 mo, this nodule showed growth by 6 mm.

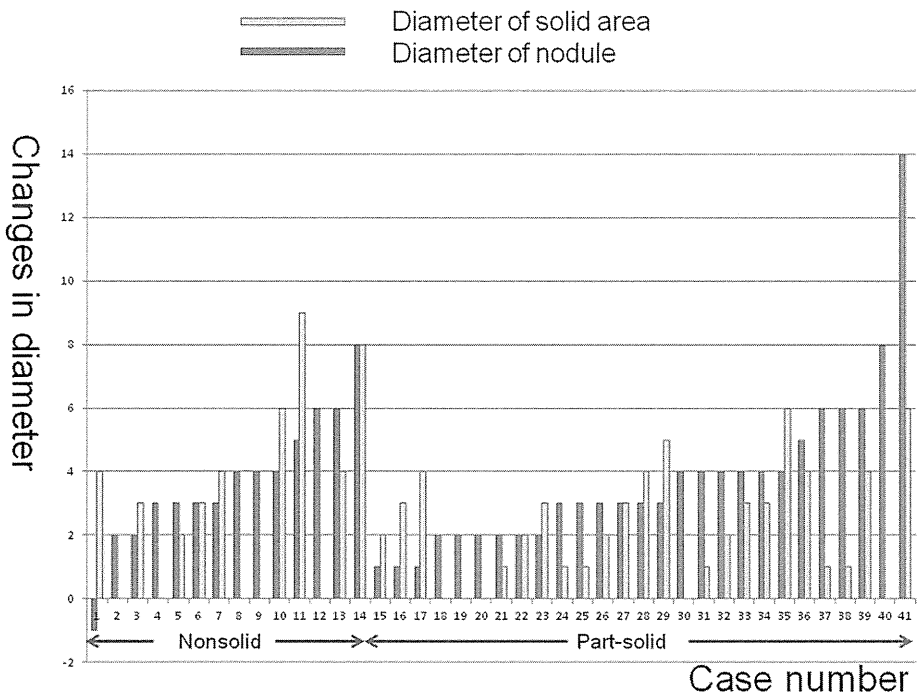

FIGURE 2. Changes in both diameter of the nodule and solid area in patients with nodules that were judged as growth. Cases are sorted according to the type of subsolid nodule and changes in nodule diameter. Dark bars represent interval size change at nodule diameter, and light bars represent interval size change at solid area.

analyses in patients with nonsolid and part-solid nodules are shown in Tables 2 and 3. Univariate analysis revealed that a lung cancer history and a nodule diameter > 10 mm for nonsolid nodules and male sex and nodule diameter > 10 mm for part-solid nodules were factors significantly associated with nodule growth. Multivariate analysis disclosed that a history of lung cancer and a nodule diameter > 10 mm for nonsolid nodules and nothing for part-solid nodules remained significant predictors of growth.

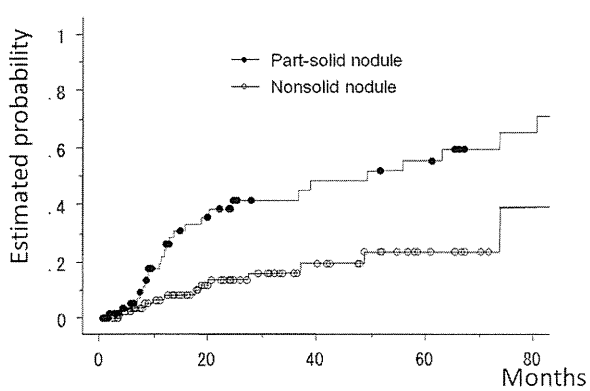

FIGURE 3. Time to 2-mm subsolid nodule growth curves according to the type of ground-glass opacity (GGO). The 2-y and 5-y cumulative percentages of a growing nodule were 13% and 23% for the nonsolid nodule, and 38% and 55% for the part-solid nodule, respectively.

During follow-up periods ranging from 3 months to 140 months, with a median period of 52 months, none of the patients experienced subsolid nodules progressing to advanced stages during follow-up with CT scanning. Only one patient experienced recurrence after surgery for part-solid nodules, and died of the disease. The patient was referred to our hospital because of three nodules, measuring 14 mm, 12 mm, and 12 mm in diameter, located in the left lower lobe of the lung. The patient had a history of lung cancer and underwent a left upper lobectomy 8 years prior to being referred to our hospital. At first, the patient refused surgical therapy. However, as follow-up CT scanning showed the growth of all three nodules, the patient underwent a basal segmentectomy. The patient experienced bone metastasis 3 months after the operation. We presumed the three nodules were not multiple primary tumors, but multiple pulmonary metastases resulting from previous lung cancer, because all three lesions showed invasiveness including vascular invasion in two lesions and pleural invasion in one lesion, in spite of their small size.

DISCUSSION

In this study, some patients underwent resection at different points of growth, and because of their older age and comorbidity, others continued to be followed

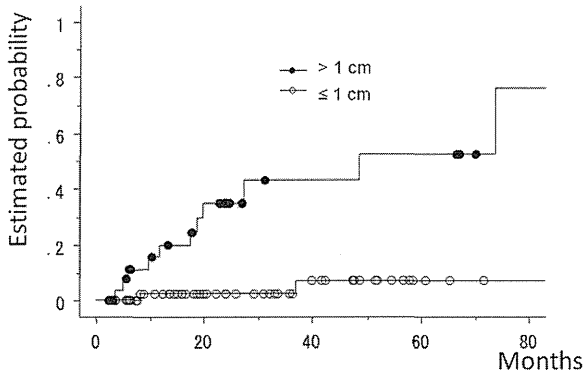

FIGURE 4. Time to 2-mm subsolid nodule growth curves according to the initial nodule diameter in patients with nonsolid nodules. The 2-y and 5-y cumulative percentages of growing nodules were 2% and 7% for nodules ≤ 10 mm, and 34% and 52% for those > 10 mm, respectively.

up in spite of growth. In this situation, we selected the Kaplan-Meier method to calculate the percentage of subsolid nodules showing growth because this method can be implemented to deal with censored cases. In the analysis with the Kaplan-Meier method, we set ≥ 2 mm growth as an event for the following reasons: a 2 mm size change is a relatively clear change in small nodules < 20 mm in diameter, with a median of 11 mm, when interval size changes were measured as described in the "Materials and Methods" section. In addition, to reduce the risk of treatment delay, a notable number of patients underwent resection at 2-mm growth. Therefore, if the event was set at a larger size, these nodules resected at 2-mm growth would be judged as showing no growth and would be censored cases. Regarding the inherent variability of reimaging, Oxnard et al[16] conducted an investigation that assessed the variability of lung tumor measurement using repeat CT scans performed within

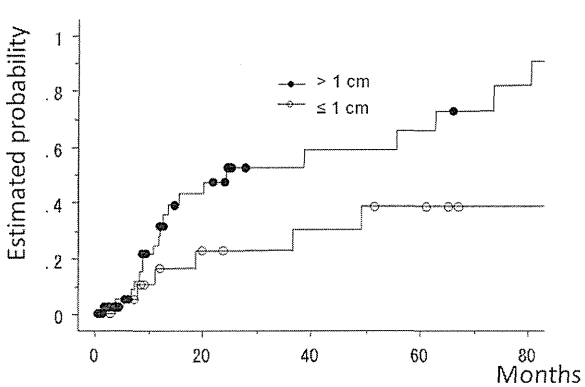

FIGURE 5. Time to 2-mm subsolid nodule growth curves according to the initial nodule diameter in patients with part-solid nodules. The 2-y and 5-y cumulative percentages of growing nodules were 23% and 38% for nodules ≤ 10 mm, and 47% and 66% for those > 10 mm, respectively.

Table 2—*Results of Univariate and Multivariate Analyses in Patients With Nonsolid Nodules*

	Univariate		Multivariate	
Variable	2 mm Growth Nodule Probability at 2 y, %	*P* Value	Hazard Ratio	*P* Value
Age, y				
≤ 60	7.9	.162	...	.442
> 60	20.0	...	1.72	...
Sex				
Female	7.0	.089	...	.355
Male	24.5	...	2.04	...
History of lung cancer				
No	7.7	.002	...	.030
Yes	42.3	...	4.03	...
Smoking history				
No	10.7	.075	...	.910
Yes	26.5	...	1.11	...
Nodule diameter				
≤ 10 mm	2.1	< .001	...	.001
> 10 mm	34.7	...	13.70	...
No. of subsolid nodules				
Solitary	11.0	.308	...	.606
Multiple	20.9	...	0.67	...

15 min of each patient. They concluded that increases and decreases of < 10% can be the result of the inherent variability of reimaging. In our current study, we analyzed nodules ≤ 2 cm in diameter; therefore, 2 mm growth represents 10% or more total growth. Furthermore, as shown in Figure 2, the majority of nodules finally exhibited growth of > 2 mm. Therefore, we believe that our determination of nodule growth represented real growth rather than inherent variability. From this analysis, we found that the time to 2 mm growth curve calculated using the Kaplan-Meier method looked similar to the logarithmic curve. The growth of subsolid nodules occurred more frequently within the first 2 years, especially in part-solid and large nonsolid nodules. This means that the follow-up interval for large nonsolid and part-solid nodules should be shorter in the first 2 years and longer thereafter. Furthermore, the growth of large nonsolid and part-solid nodules occurred even after 5 years. Therefore, the follow-up of subsolid nodules is thought to be necessary throughout the patient's life, especially for large subsolid nodules, and follow-up intervals should be determined considering radiation exposure during CT scan examination.

The current investigation revealed that part-solid nodules had a greater growth tendency compared with nonsolid nodules. In addition, this study highlighted two independent factors associated with the growth of nonsolid nodules: a large initial nodule diameter and history of lung cancer. The interval change of subsolid

Table 3—*Results of Univariate and Multivariate Analyses in Patients With Part-Solid Nodules*

Variable	Univariate		Multivariate	
	2 mm Growth Nodule Probability at 2 y, %	*P* Value	Hazard Ratio	*P* Value
Age, y				
≤ 60	31.3	.407	...	.902
> 60	44.1	...	1.06	...
Sex				
Female	26.9	.016	...	.160
Male	58.4	...	2.17	...
History of lung cancer				
No	36.6	.870	...	.798
Yes	44.4	...	1.14	...
Smoking history				
No	33.8	.216	...	.743
Yes	47.4	...	0.84	...
Nodule diameter				
≤ 10 mm	22.7	.021	...	.099
> 10 mm	47.3	...	2.30	...
No. of subsolid nodules				
Solitary	38.7	.581	...	.403
Multiple	37.0	...	0.67	...

nodules was first reported by Hasegawa et al.[3] They analyzed 19 nonsolid and 19 part-solid nodules. Their analysis demonstrated that the volume doubling time of nonsolid nodule was significantly longer than that of the part-solid nodule (813 days vs 457 days, respectively). Lee et al[10] and Sawada et al[9] also found that the part-solid nodule was associated with the growth of nodules compared with nonsolid nodules. They reported that 17.4% of nonsolid nodules and 32.0% of part-solid nodules showed growth. Hiramatsu et al[8] analyzed 125 subsolid nodules which were stable during follow-up CT scan carried out for a period of at least 3 months. Their statistical analysis revealed that not a part-solid nodule, but a large nodule size and history of lung cancer were independent factors associated with the growth of subsolid nodules. Although a large nodule size and part-solid nodules can be easily associated with the growth, a lung cancer history is difficult to link to the growth of subsolid nodules. Hiramatsu et al[8] speculated on two possible explanations. The first explanation is that newly developing subsolid nodules are intrapulmonary metastases from previous lung cancer. The second is that these subsolid nodules are metachronous second primary lesions with a more aggressive nature and faster speed of growth. We concur with both hypotheses. In our investigation, we believe that at least one of the patients had multiple pulmonary metastases rather than multiple primary lung cancer, as described in our results. However, we do not think that most of the subsolid nodules associated with a lung cancer history were pulmonary metastasis because no other patient experienced recurrence. It is possible that patients with a history of lung cancer have genetic damage of the entire lung. Therefore, although similar in appearance, subsolid nodules which emerge in patients with or without a lung cancer history may be associated with different genetic changes and demonstrate varied growth tendencies.

Care should be taken in interpreting our results on part-solid nodules because only selected patients were followed. As mentioned in the "Materials and Methods" section, we usually recommend an immediate diagnostic procedure and resection instead of follow-up with CT scanning for patients with part-solid nodules suspected of being lung cancer. Therefore, there were some occasions to select follow-up with CT scanning. One was suspected cases of an inflammatory process rather than lung cancer. After a short period of follow-up, if they showed no interval change and were suspected of showing an old inflammatory process, we continued follow-up with CT scanning until some changes were detected or for > 2 years. The other was cases of part-solid nodules but showing a wide area of GGO. In fact, 52% of part-solid nodules showed more than a 90% GGO area. These nodules have been analyzed in combination with nonsolid nodules in several studies.[19,20] We thought that these nodules may act similarly to nonsolid nodules. The remaining included an older age and comorbidity. These background factors should be considered in interpreting data on mixed GGO cases.

One concern regarding follow-up with CT scan is a possible delay in treatment.[9] Follow-up with CT scanning allows the slight growth of nodules. Whether this slight growth can change the patient's prognosis is unknown. However, we believe that this type of disadvantage is much smaller for subsolid than solid nodules. This is because patients who have nodules that show extensive areas of GGO, usually >50%, have been reported to be curable at a rate of almost 100% when treated surgically.[19,21,22] Therefore, in patients with growing subsolid nodules containing extensive areas of GGO, follow-up with CT scanning may not influence the prognosis. In the current study, no patient experienced recurrence or metastasis except one case with a 23% GGO area in the nodule. The patient was also thought to have pulmonary metastases from previous lung cancer rather than primary multiple lung tumors, as described in "Results." Therefore, possible disadvantages may focus on a sudden rapid growth to an incurable stage during follow-up CT scanning. To determine the frequency of the abrupt growth of subsolid nodules, we searched for such cases in the literature, and found only one similar case reported in Japanese.[23] This case was not a real scheduled

follow-up case, and, based on the results of our study and literature review, we hypothesize that the percentage of subsolid nodules showing sudden growth during scheduled follow-up is extremely low. As we recognize that the true frequency of the unexpected growth of subsolid nodules during follow-up with CT scanning should be determined prospectively, our group is prospectively registering patients with subsolid nodules at multicenter.

In conclusion, subsolid nodules show different natural histories: some subsolid nodules show growth, some show shrinkage, and some remain stable for long periods. Factors associated with growth are the type of subsolid nodule, initial nodule size, and history of lung cancer. Intervals of follow-up CT scanning for subsolid nodules should be determined considering these factors. In addition, the growth of subsolid nodules can occur after a long period, especially in large tumors and those with a solid component. Therefore, if subsolid nodules are followed with CT scanning, lifelong follow-up may be needed. In this situation, appropriate, long interval periods to reduce radiation exposure due to CT scan examination will also become important.

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Dr Matsuguma: contributed to study design, data acquisition, and manuscript preparation.
Dr Mori: contributed to manuscript preparation and read and approved the final manuscript.
Dr Nakahara: contributed to manuscript preparation and read and approved the final manuscript.
Dr Suzuki: contributed to manuscript preparation and read and approved the final manuscript.
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Modern surgical results of lung cancer involving neighboring structures: A retrospective analysis of 531 pT3 cases in a Japanese Lung Cancer Registry Study

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Objective: The aim of the present study was to identify the modern surgical results of pathologic T3 lung cancer and to examine the heterogeneity of this group from the nationwide database.

Methods: The registered data of 11,663 cases from the Japanese Joint Committee of Lung Cancer Registry conducted in 2010 were analyzed, which included patients with resected lung cancer during 2004. Of these patients, 531 with invasive T3 lung cancer constituted the study population.

Results: Of the 531 patients, 466 were men and 65 women, with a mean age of 65.9 years. The 3- and 5-year survival rates and median survival time was 54.0%, 44.9%, and 46 months, respectively. A multivariate analysis showed incomplete resection, N2 disease, and no adjuvant therapy were independent prognostic factors of a poor outcome. However, pneumonectomy and N1 disease were not significantly associated with the prognosis. In terms of each involved structure, we detected 407 patients with T3 tumors involving the chest wall, 56 involving the mediastinal pleura, 45 with involvement of the bronchus within 2 cm of the carina, 31 involving the diaphragm, and 20 involving the pericardium. The corresponding 5-year survival rates were 43.2%, 40.1%, 55.2%, 42.6%, and 54.2%.

Conclusions: The modern 5-year survival rates of patients with T3 lung cancer involving any neighboring structures have been 40% to 55%, and the current pT3 group was proved to have a relatively uniform prognosis. (J Thorac Cardiovasc Surg 2012;144:431-7)

Extended surgical resections are still frequently used for the treatment of patients with locally advanced lung cancer involving a neighboring structure. From the report on the nationwide retrospective registry study of primary lung cancer conducted by the Japanese Joint Committee of Lung Cancer Registry in 2010, there were 1013 combined resections (8.7%) with neighboring structures in 2004, although the number was smaller than that in 1999 (n = 1480 [11.1%]).[1]

The TNM staging system for lung cancer was revised and promulgated in 2009; however, the distribution of involved organs for the staging between T3 and T4 remained unchanged.[2] T3 lung cancers with limited, circumscribed extrapulmonary extension are considered to be potentially resectable, and the efficacy of surgical treatment for T3 lesions is generally accepted. However, the surgical results for such advanced tumors have not been satisfactory, and there has been heterogeneity in the reported prognoses depending on the structure involved.[3] The aim of the present study was to identify the modern surgical results of pathologic T3 lung cancer with involvement of neighboring structures, to examine the heterogeneity of this group from the nationwide database, and to discuss the direction of surgical resection for locally advanced lung cancer.

METHODS

A nationwide retrospective registry study of patients with primary lung cancer who underwent surgery from January 1, 2004, to December 31,

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2004, was performed by the Japanese Joint Committee of Lung Cancer Registry in 2010. The committee received the registries of 11,663 cases from 253 teaching hospitals in Japan. The data included the clinicopathologic profiles and prognoses, which had been described previously.[1] The information regarding the TNM classification was converted to the 7th edition of the International Union Against Cancer-TNM staging system published in 2009.[2] The histologic tumor type was described according to the World Health Organization.[4]

The present study focused on pathologically confirmed invasive T3 lung cancer involving the chest wall, mediastinal pleura, bronchus within 2 cm of the carina, diaphragm, or pericardium. Ineligible patients, such as those who underwent exploratory thoracotomy (n = 6), had small cell carcinoma histologic features (n = 13), low-grade malignant histologic features (n = 7), or distant metastasis (n = 22), were excluded from the present study. Superior sulcus tumors, defined as those with first rib involvement in this registry study, were not extracted from the cohort when they were categorized pathologically as T3 according to the TNM staging system (n = 10). Therefore, 531 cases were enrolled in the present study, with a follow-up period of at least 5 years after surgery.

The survival time was measured from the date of surgery to the date of death or the last follow-up examination. The survival curves were estimated using the Kaplan-Meier method, and the differences in survival were assessed using the log-rank test. A multivariate analysis for prognostic factors was performed using the Cox proportional hazard model.

This registry followed the ethical guidelines for epidemiologic studies published jointly by the Japan Ministry of Science, Culture, and Education and the Japan Ministry of Health, Labor, and Welfare on June 17, 2002, and revised August 16, 2007. In addition, the institutional review board of Osaka University Medical Hospital, where the registry office is located, approved the study, after the discussions published August 13, 2009 (approval no. 09124). All statistical analyses were performed independently by the biologic statistician (E.M.).

RESULTS

The characteristics of the 531 included patients with invasive T3 lung cancer are listed in Table 1. Of the 531 patients, 466 were men and 65 were women, with a mean age of 65.9 years (range, 37-83). In terms of tumor histologic type, squamous cell carcinoma was the most common, followed by adenocarcinoma. From the pathologic examinations, 461 patients (86.8%) underwent complete resection of the lung and involved structures. Of all cases, 34% were pathologically confirmed as lymph node-positive. Induction therapy was performed in 89 cases (16.8%), including 46 cases of chemoradiotherapy, 35 of chemotherapy, and 8 of radiotherapy. Adjuvant chemotherapy was administered to 177 patients, intravenously in 110, orally in 57, and by other routes in 10. No data were available on postoperative radiotherapy. Stratified by the involved structures, the chest wall (including parietal pleura only) was the most common, present in up to 76.6% of cases, followed by the mediastinal pleura (10.6%), bronchus (8.5%), diaphragm (5.8%), and pericardium (3.8%).

The overall survival curve for all 531 patients with invasive T3 lung cancer is shown in Figure 1. The 3- and 5-year overall survival rate after surgery was 54.0% and 44.9%, respectively, and the median survival time was 46 months.

TABLE 1. Patient characteristics

Variable	Value
Age (y)	
Mean	65.9
Range	37-83
Gender	
Male	466 (87.8)
Female	65 (12.2)
Histologic type	
Squamous cell carcinoma	250 (47.1)
Adenocarcinoma	201 (37.9)
Large cell carcinoma	45 (8.5)
Adenosquamous carcinoma	15 (2.8)
Other	20 (3.8)
Surgical procedure	
Lobectomy	430 (81.0)
Pneumonectomy	63 (11.9)
Other	38 (7.1)
Residual tumor	
R0	461 (86.8)
R1	48 (9.0)
R2	16 (3.0)
Rx	6 (1.1)
Nodal status	
N0	351 (66.1)
N1	81 (15.3)
N2	98 (18.5)
N3	1 (0.2)
Induction therapy	
Yes	89 (16.8)
No	442 (83.2)
Adjuvant chemotherapy	
Yes	177 (33.4)
No	323 (60.8)
Unknown	31 (5.8)
Involved structure	
Chest wall	407 (76.6)
Mediastinal pleura	56 (10.6)
Bronchus	45 (8.5)
Diaphragm	31 (5.8)
Pericardium	20 (3.8)

Data presented as numbers, with percentages in parentheses.

The surgical mortality rate within 30 days postoperatively was 1.1%, and the total in-hospital death rate was 3.2%. Survival according to various factors in the patients with invasive T3 lung cancer is detailed in Table 2. No significant differences were seen in survival between the men and women, those with squamous cell carcinoma versus adenocarcinoma, nor in those who underwent lobectomy versus pneumonectomy ($P = .078$). A pathologically complete resection (R0) resulted in markedly better survival than an incomplete resection (R1+R2; Figure 2, *A*; $P < .001$). When stratified by nodal status, the 351 patients with N0 disease and 81 with N1 disease had a significantly better prognosis than the 98 with N2 disease (5-year survival rate; 50.6% and 46.3% vs 22.0%, $P < .001$ and $P = .002$, respectively).

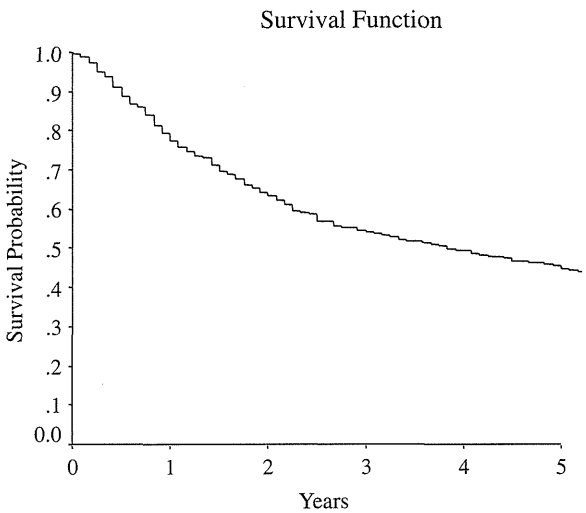

FIGURE 1. Overall survival curve for patients with invasive T3 lung cancer; 3- and 5-year survival rates and median survival time was 54.0%, 44.9%, and 46 months, respectively.

No significant difference was seen between patients with N0 and N1 disease ($P = .436$, Figure 2, *B*). When stratified by perioperative therapy, adjuvant chemotherapy proved to be a significant prognostic factor ($P = .006$, Figure 2, *C*), but induction therapy was not ($P = .409$). Multivariate analysis showed incomplete resection, N2 disease, and no adjuvant therapy to be independent prognostic factors for a poor outcome, but pneumonectomy and N1 disease were not significantly associated with the prognosis (Table 3).

The 3- and 5-year survival rates with the median survival time of patients with lung cancer involving each structure are listed in Table 4. Patients with bronchial invasion had a better prognosis than those with the involvement of other structures. Of the patients with T3 cancer and chest wall invasion, those with N0 disease tended to have better survival than those with N1 disease ($P = .055$) and had a significantly better survival than those with N2 disease ($P < .001$). However, no significant difference was seen in survival between patients with N1 and N2 disease ($P = .144$; Figure 3). The 5-year survival rate of those with N2 disease involving the mediastinal pleura was only 9.8%, significantly poorer than the survival of those with N0 and N1 ($P = .026$ and $P = .001$, respectively).

Only 1 patient died during the 5 years after surgery among the 19 patients with bronchial invasion and without lymph node involvement. However, no significant difference was seen in survival between those with N1 and N2 disease ($P = .594$). For the patients with T3 disease and diaphragmatic invasion, the 5-year survival rate of those with N0 was 55.0%, comparable to that of the patients with N0 disease and chest wall or pericardial involvement.

TABLE 2. Survival rates according to each factor

Variable	3-y survival (%)	5-y survival (%)	MST (mo)	*P* value
Gender				NS
Male	53.6	44.7	45	
Female	57.5	46.2	53	
Histologic type				NS
Squamous cell carcinoma	52.6	45.5	43	
Adenocarcinoma	58.6	45.1	50	
Other	47.0	41.8	27	
Surgical procedure				NS
Lobectomy	55.3	46.2	50	
Pneumonectomy	44.5	35.4	27	
Other	56.2	46.4	41	
Residual tumor				<.001
R0	57.8	47.5	54	
R1+R2	26.1	24.2	19	
Nodal status				NS*; <.001†; .002‡
N0	60.6	50.6	62	
N1	53.3	46.4	49	
N2	30.3	22.0	21	
Induction therapy				NS
Yes	56.4	50.0	60	
No	53.6	43.8	44	
Adjuvant chemotherapy				.006
Yes	62.8	51.8	62	
No	49.1	41.1	35	

MST, Median survival time; *NS*, no significance. *N0 vs N1. †N0 vs N2. ‡N1 vs N2.

Nevertheless, the survival of those with N1 and N2 disease was much poorer than that of those with N0 disease (N0 vs N1, $P = .044$; N0 vs N2, $P = .031$, respectively), although only a few patients had nodal involvement. Patients with pericardial invasion were the most infrequently found in the present series, and their prognosis was relatively good despite the positive nodal status.

Additional analyses were done concerning the prognosis of patients with T3 disease and chest wall invasion. Of the 299 patients with N0 disease, 264 (88.3%) underwent complete resection with no residual tumor after pathologic examination. Of these, 119 patients had invasion only to the parietal pleura and 145 had substantial chest wall involvement. Their survival curves are presented in Figure 4. No significant difference was seen in survival between those with shallow versus deep invasion, with a 5-year survival rate of 50.6% and 48.7%, respectively ($P = .702$). In addition, extrapleural resection was performed in 82 cases and en bloc chest wall resection in 22 cases for T3N0 lung cancer invading only the parietal pleura. No significant difference was seen in survival according to the extent of chest wall resection for patients with shallow invasion to the chest wall ($P = .733$, Figure 5).

GTS

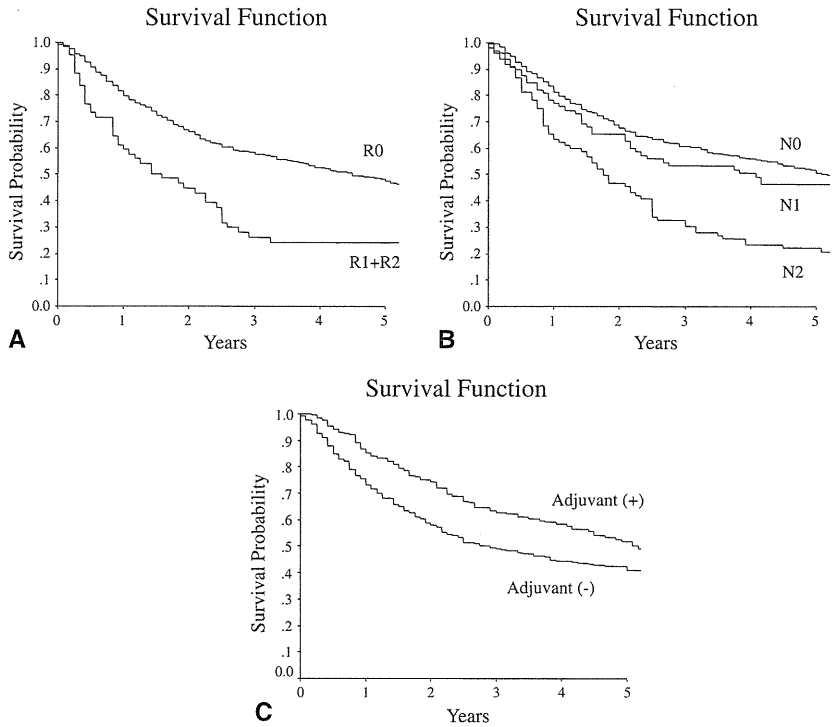

FIGURE 2. Overall survival curves according to (A) residual tumor, (B) nodal status, and (C) use of adjuvant therapy in patients with invasive T3 lung cancer. A, Complete resection resulted in markedly better survival than incomplete resection ($P < .001$). B, 351 N0 and 81 N1 patients had a significantly better prognosis than the 98 N2 patients (5-year survival, 50.6% and 46.3% vs 22.0%; $P = .000$ and $P = .002$, respectively), and no significant difference was seen between the N0 and N1 patients ($P = .436$). C, Adjuvant chemotherapy was proved to be a significant prognostic factor ($P = .006$).

GTS

DISCUSSION

A number of reports have been published concerning the surgical results for invasive T3 lung cancers from several institutions. However, they have often included consecutive cases over a long period, and the outcomes were somewhat nebulous.[3,5,6] The present study reports on surgical cases treated within 1 year and followed up for more than 5 years. In addition, the present study evaluated T3 tumors according to the involved sites, in contrast to the International Association for the Study of Lung Cancer staging project, which did not.[7] Therefore, the present study provides accurate modern surgical results of a large number of cases and the prognosis stratified by each involved structure from the nationwide database.

TABLE 3. Multivariate analysis of prognostic factors in patients with invasive T3 lung cancer

Variable	Reference	HR	95% CI	*P* value
Surgical procedure (pneumonectomy)	Other procedures	0.863	0.584-1.275	.459
Residual tumor (R1+R2)	R0	2.007	1.432-2.814	<.001
Nodal status (N1)	N0	1.156	0.790-1.692	.455
Nodal status (N2)	N0	2.212	1.636-2.991	<.001
Adjuvant chemotherapy (yes)	No	0.575	0.439-0.753	<.001

HR, Hazard ratio; *CI,* confidence interval.

Complete resection and lymph node metastasis have been reported as implicit prognostic factors for patients with locally advanced lung cancer, and our results have also confirmed this trend. However, it was surprising that no significant difference was seen in survival between patients with T3N0 and T3N1 tumors ($P = .436$), and the 5-year survival rate of the latter group was 46.4%. This relatively good outcome seems to have been because many of the T3N1 tumors infiltrating central structures such as the mediastinal pleura, main bronchus, or pericardium contributed to the favorable prognosis.

The common belief that "pneumonectomy is a disease" was not proved to be true in the present cohort.[8,9] Multivariate analysis showed that the surgical procedures used for lung resection were not a significant prognostic factor, although T3 lung cancer involving various structures were included in the present analysis. Although 26 patients had bronchial invasion less than 2 cm from the carina, these patients were not a majority in the pneumonectomy group. Recent series have shown the feasibility of pneumonectomy

TABLE 4. Survival rates according to each structure

Involved structure	Patients (n)	3-y survival (%)	5-y survival (%)	MST (mo)
Chest wall				
All	407	51.6	43.2	42
N0	299	58.3	49.1	60
N1	43	42.3	36.5	28
N2	65	27.3	20.5	20
Mediastinal pleura				
All	56	56.7	40.1	46
N0	23	62.6	37.9	46
N1	13	84.6	76.2	NR
N2	19	26.0	9.8	21
Bronchus				
All	45	64.4	55.2	NR
N0	12	100	91.7	NR
N1	22	54.6	45.5	45
N2	11	45.5	36.4	31
Diaphragm				
All	31	49.7	42.6	35
N0	20	65.0	55.0	65
N1	3	0	0	10
N2	8	18.8	18.8	11
Pericardium				
All	20	54.2	54.2	63
N0	8	50.0	50.0	13
N1	5	80.0	80.0	NR
N2	7	38.1	38.1	31

MST, Median survival time, *NR,* not reached.

after induction therapy without excessive morbidity. The findings of the present study are thus considered to follow the modern consensus that "pneumonectomy is feasible for selected cases."[10] It is suspected that the improvements in anesthesiology and perioperative care and strict patient selection resulted in the better survival of patients who underwent extended resection.

Regarding perioperative therapies, adjuvant chemotherapy has been proved to be effective for whole stage II and IIIA cases.[11,12] In the present study, adjuvant chemotherapy was also effective when targeted toward T3 disease. However, detailed information, such as the indications, chemotherapy regimen, dose intensity, and so forth, were

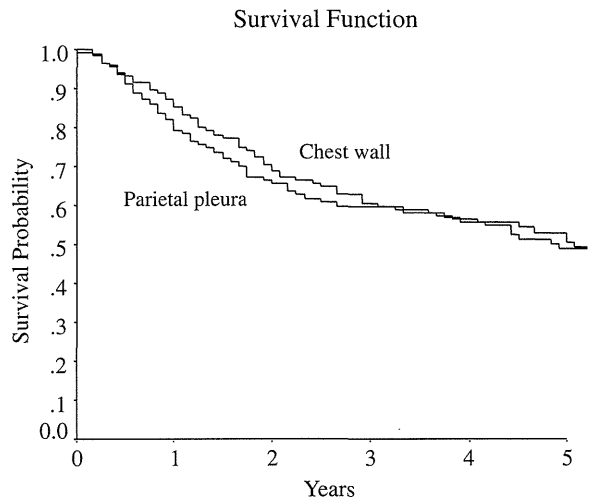

FIGURE 4. Overall survival curves according to depth of invasion in patients with completely resected T3N0 lung cancer involving the chest wall. No statistically significant difference was observed in survival between the 2 groups ($P = .702$).

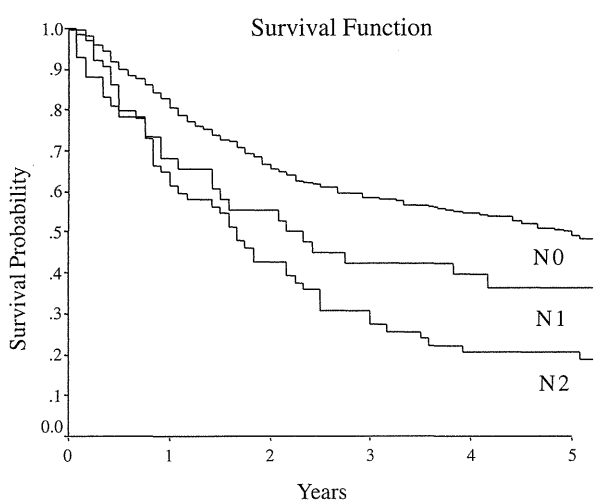

FIGURE 3. Overall survival curves according to nodal status for patients with lung cancer involving the chest wall. Patients with N0 disease tended to have better survival than those with N1 disease ($P = .055$), and they also had significantly preferable survival compared with those with N2 disease ($P < .001$).

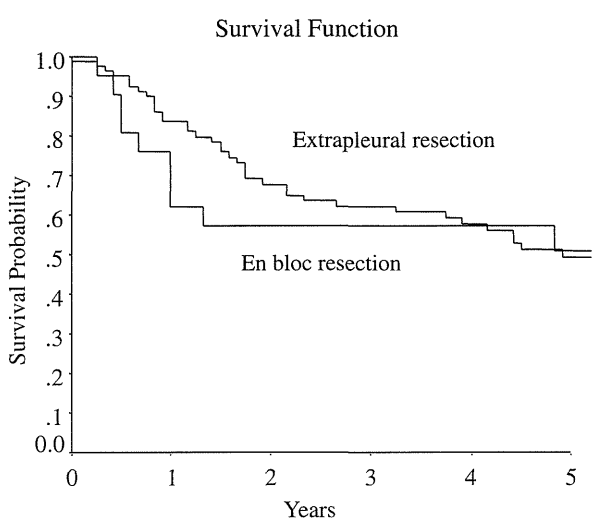

FIGURE 5. Overall survival curves according to extent of combined resection in patients with completely resected T3N0 lung cancer involving the parietal pleura. No significant difference was seen in survival according to extent of chest wall resection ($P = .733$).

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not available in this registry. A couple of investigators have advocated the usefulness of adjuvant radiotherapy for invasive T3 tumors.[6,13] However, information on radiotherapy was not collected in the present registry study. Induction therapy followed by surgery has become a standard strategy for superior sulcus tumors; however, only a few reports have been published on its use for other T3 tumors.[14,15] Therefore, additional investigation of the individual tumor types will be needed in the future.

The chest wall is the most common site infiltrated by peripheral lung cancer. A number of investigators have described the prognostic factors of the disease.[16,17] However, it is still controversial whether the depth of invasion or the extent of combined resection influences patient survival.[16,17] Patients with the chest wall invasion underwent complete resection and had N0 disease, and we found no statistically significant differences according to the depth of the tumor invasion with respect to survival. In addition, among patients with tumor invasion only to the parietal pleura, extrapleural resection and en bloc chest wall resection resulted in similar survival rates. Doddoli and colleagues[6] demonstrated that en bloc resection was associated with a significantly better prognosis from the viewpoint of safety margins for patients with invasion limited to the parietal pleura. In contrast, some investigators have recommended extrapleural resection for patients with invasion limited to the parietal pleura because of the lower mortality or morbidity rates.[18,19] In the present study, extrapleural resection was generally selected for lung cancer with shallow invasion, and the results have shown that experienced surgeons made the correct judgment regarding the extent of combined resection for these cases.

Of the various involved structures, the main bronchus was related to the best prognosis, as previously reported.[3,20] Only 1 patient of those with bronchogenic carcinoma, invasion less than 2 cm from the carina, and had no lymph node metastasis died during the follow-up period. Thus, the T3 criterion of tumor in the main bronchus less than 2 cm distal to the carina could be re-evaluated.

Lung cancer with diaphragmatic invasion is currently categorized as a T3 tumor; however, it has been suggested that the disease should be reclassified as T4 because of its poorer prognosis.[21,22] In the 7th edition of the AJCC Cancer Staging Handbook states that the classification of diaphragmatic invasion might need to be re-evaluated in the future as more survival data become available.[23] Despite these arguments, the present study has demonstrated that patients with lung cancer and pathologically proven diaphragmatic invasion and N0 disease had similar prognoses compared with other T3N0 cases. Although only 20 cases were in the present study, limiting the conclusions that can be drawn, it is possible that diaphragmatic invasion is suitable for T3 classification because of the improvements in perioperative factors.

The prognosis of patients with T3 tumors involving the pericardium was relatively good, regardless of nodal status. Sakakura and colleagues[3] reported the 5-year survival rate of 14 patients who underwent resection of tumor invading the pericardium, including 5 patients with N2 disease, was 21.4%. The current result could still be equivocal because the number of patients was small (n = 20) in our study population, and only a few studies have addressed the prognosis of those patients.

Our study had several limitations. This was a retrospective study, and the cases were accumulated from a large number of institutions, which could have resulted in institutional diversity in the surgical procedure and management and the indications for perioperative therapies. In addition, some information was lacking in the registry, such as the use of postoperative radiotherapy and tumor differentiation. Finally, 18 patients had invasion in more than 1 structure. The 5-year survival rate and median survival time of that group was 28.9% and 21 months, respectively, worse than those of the patients with involvement of a single structure. However, such overlapping occurred in a very small number of patients and even included patients with 3 involved organs. Therefore, we analyzed the prognostic factors for all patients with T3 invasive lung cancer.

CONCLUSIONS

The modern 5-year survival rates of patients with T3 lung cancer involving any neighboring structures from the present nationwide study were 40% to 55%. Our study also provided additional valuable information. The current pT3 group with involvement of various structures was found to have a relatively uniform prognosis, although more survival data should be collected for the next TNM staging revision.

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Surgical Outcome of Stage IIIA- cN2/pN2 Non–Small-Cell Lung Cancer Patients in Japanese Lung Cancer Registry Study in 2004

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Background: The role of surgery in the treatment of non–small-cell lung cancer (NSCLC) with clinically manifested mediastinal node metastasis is controversial even in resectable cases because it is often accompanied by systemic micrometastasis. However, surgery is occasionally indicated for cases with single-station N2 disease or within multimodal treatment regimens, and in clinical trials. The aim of this study is to evaluate surgical outcomes in a modern cohort of patients with clinical (c-) stage IIIA-N2 NSCLC whose nodal metastasis was confirmed by pathology (cN2/pN2).

Methods: From the central database of lung cancer patients undergoing surgery in 2004, which was founded by the Japanese Joint Committee for Lung Cancer Registration, data of patients having all conditions of NSCLC, c-stage IIIA, cN2, and pN2 were extracted, and the clinicopathologic profile of patients and surgical outcomes were evaluated.

Results: Among 11,663 registered NSCLC cases, 436 patients (3.8%) (332 men and 104 women) had been extracted. Their mean age was 65 years, and histologic types included adenocarcinoma (n = 246), squamous cell carcinoma (n = 132), and others (n = 58). The proportion of R0 resection was 82.5% and the proportion of the hospital deaths among the cause of death was 2.3%. The 5-year survival rate was 30.1% for the selected group of patients. The postoperative prognosis was significantly better than those of corresponding populations extracted from the 1994 ($p = 0.0001$) and 1999 databases ($p = 0.0411$). Men and women experienced a significantly different survival outcome ($p = 0.025$) with 5-year survivals of 27.5% and 37.8%, respectively. Single-station N2 cases occupied 60.9 % of the cohort and showed a significantly better prognosis than multistation N2 ($p = 0.0053$, 35.8 % versus 22.0 % survival rate at 5 years).

Conclusions: The surgical outcomes of c-stage IIIA-cN2/pN2 NSCLC patients in 2004 were favorable in comparison with those ever reported.

Key Words: Non–small-cell lung cancer, Mediastinal node metastasis, Surgery.

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Surgery is not a generally accepted option for non–small-cell lung cancer (NSCLC) patients with clinically manifested mediastinal lymph node metastasis (cN2/pN2), because the presence of N2 metastasis is believed to be indicative of systemic disease. In reports published in the 1980s through the early 1990s,[1–4] surgery for c-stage IIIA-N2 often failed to result in local control and was often followed by early appearance of distant metastasis, even after complete resection. Since the 1990s, numerous researchers have reported clinical trials of induction chemotherapy or chemoradiotherapy followed by surgery[5–8]; however, the role of surgery in the treatment strategy for the disease is still controversial. A recent large-scale trial, the North American Intergroup Trial 0139,[9] demonstrated that surgery after induction chemoradiotherapy can be beneficial if lobectomy is adequate for complete resection, although overall survival (the primary end point) in the trimodal regimen group was equivalent to that in the chemoradiotherapy group. Adjuvant chemotherapy is another potential option; however, whether cN2/pN2 cases derive the same

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survival benefit from adjuvant chemotherapy as that reported for cN0-1pN2 cases has not yet been clarified.[10,11]

In Japan, a nationwide database has been managed by the Japanese Joint Committee of Lung Cancer Registration since 1989. Annual surgical series are collected at 5-year intervals, and surgical outcomes have been analyzed and reported.[12–14] Since then, there has been an increase in the proportions of patients who are women, have stage IA disease and adenocarcinoma, and 5-year survival rates have gradually improved from 52.6% in 1994,[12] to 61.8% in 1999,[13] and to 69.7% in 2004.[14] Such results clearly indicate that the clinical profile of lung cancers is dramatically changing in Japan. If so, and even if progress in radiological work-up biases candidates for surgery, the surgical outcomes of a modern series of c-stage IIIA-cN2/pN2 NSCLC patients should be reevaluated. In this study, stage III NSCLC patients with clinically manifested and pathologically proven N2 were collected from a nationwide registry data of resected lung cancer in Japan, and retrospectively investigated.

PATIENTS AND METHODS

Patients

In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective survey for primary lung neoplasms resected in 2004. Data from 11,663 patients who were followed up for 5 years were registered from 253 teaching hospitals. Of these patients, data from those with all conditions of histologically confirmed NSCLC, c-stage IIIA, cN2, and pN2 were extracted from the master database, and the clinicopathologic profiles of patients and surgical outcomes were evaluated. In addition, the data were compared to those of similar populations from the 1994 and 1999 databases. The c-stage and p-stage were determined according to the 6th edition of the Union Internationale Contre le Cancer-TNM staging system,[15] and tumor histology was categorized according to the World Health Organization Classification.[16] A number of mediastinal node stations where metastases were recognized by surgical pathology were classified as single- or multistation. Each nodal station was determined according to Naruke's map.[17]

Statistical Analysis

Differences in clinicopathologic demographic variables were evaluated by the χ^2 test or Fisher's exact test as appropriate. The survival time was defined as time from the date of surgery to the date of the last follow-up. The survival curves were estimated by the Kaplan-Meier method. Differences in survival were assessed by the log-rank test. A multivariate analysis for prognostic factors was performed by the Cox proportional hazards regression model. Statistical significance was considered to be established when the associated p-value was less than 0.05.

TABLE 1. Demographic Data of c-stage IIIA-cN2/pN2 Patients

Category	Number of Patients (%)		
Year of Registry	2004	1999	1994
Total	436 (100)	823 (100)	580 (100)
Sex			
Male	332 (76.1)	633 (78.0)	438 (75.5)
Female	104 (23.9)	179 (21.7)	141 (24.3)
Unknown		11	1
Age (yrs)			
59	107 (24.7)	214 (26.0)[a]	167 (28.8)[b]
60–69	152 (34.9)	321 (39.0)	225 (38.8)
70–79	156 (35.8)	249 (30.3)	179 (30.9)
80	21 (4.8)	21 (2.6)	8 (1.4)
Unknown		18	1
Histologic type			
Adeno	246 (56.4)	458 (55.7)[a]	291 (50.2)[b]
Squ.	132 (30.2)	290 (35.2)	232 (40.0)
Other	58 (13.3)	75 (9.1)	57 (9.8)
cT-factor			
T1	137 (31.4)	183 (22.2)[b]	112 (19.3)[b]
T2	226 (51.8)	490 (59.5)	349 (60.2)
T3	73 (16.7)	150 (18.2)	119 (20.5)
pT-factor			
T0-1	116 (26.6)	161 (25.0)[a]	98 (17.0)[b]
T2	203 (46.6)	410 (49.8)	286 (49.6)
T3	68 (15.6)	118 (14.3)	92 (15.9)
T4	49 (11.2)	123 (14.9)	101 (17.5)
Unknown			3
Type of surgery			
Pn.	46 (10.6)	115 (14.0)[b]	114 (19.8)[b]
Lob./bilob.	332 (76.1)	656 (80.6)	442 (76.7)
Sublob.	30 (6.9)	41 (5.0)	20 (3.4)
Other	28 (6.4)[c]	2 (0.2)	0 (0.0)
Unknown		11	4
Residual disease			
R0	353 (82.5)	661 (80.3)	443 (77.4)
R1/2	75 (17.5)	130 (19.7)	120 (21.0)
Unknown	8	32	17
Perioperative treatment			
Induction	108 (24.8)[d]	141 (17.4)	53 (9.1)
Adjuvant[e]	151 (34.6)	—	—
None	137 (31.4)	—	—
Cause of death			
All	278 (63.8)	539 (65.5)	446 (76.9)
Hospital	10 (2.3)	30 (3.6)	32 (5.5)
Lung cancer	241 (55.3)	445 (54.1)	366 (63.1)
Other	27 (6.2)[f]	59 (7.2)	43 (7.3)

[a]Statistically significant difference ($p < 0.05$) compared to 2004.
[b]Statistically significant difference ($p < 0.01$) compared to 2004.
[c]Includes 20 exploratory thoracotomies.
[d]Eighty-four patients received chemotherapy, 23 received chemoradiotherapy, and 1 received other radiotherapy.
[e]Thirty-eight patients received oral chemotherapy.
[f]Includes deaths related to other cancers (n = 7), deaths related to noncancerous disease (n = 18), and deaths with unknown causes (n = 2).

RESULTS

Patient Profiles

Among 11,663 registered lung cancer patients, 800 cases of c-stage IIIA/ cN2/NSCLC were included. Of them, p-N0, 1, 2, and 3 were 271, 75, 436, and 18 patients, respectively, and the 436 cN2/pN2 patients were analyzed in this study. Patients with single- and multistation N2 were 235 and 151, respectively, and no information was available in the other 34. Demographic data for the patients are summarized in Table 1. These patients represented 3.8% of all 11,423 NSCLC patients in the 2004 registry, and comprised 332 men and 104 women. The mean age was 65.0 years, and 40.6% of patients were 70 years old or more. Histologic types include adenocarcinoma (n = 246), squamous cell carcinoma (n = 132), large cell carcinoma (n = 23), adenosquamous cell carcinoma (n = 17), and others (n = 18). Induction treatments such as chemotherapy and chemoradiotherapy were administered to 108 patients (24.8%), and adjuvant chemotherapy including oral tegafur/ uracil was given to 151 patients (34.6%). Surgical procedures included pneumonectomy (n = 46), lobectomy/bilobectomy (n = 332), sublobar resection (n = 30), and exploratory thoracotomy (n = 20); R0 surgery was achieved in 361 patients (82.5%). Overall, 278 patients died during the 5-year follow-up period. Of these, 10 deaths (2.3%) occurred in the hospital after surgery and 6 deaths (1.4%) occurred within 30 days after surgery. Patient profiles were compared to those of patients with the same disease stage from previous registry data (Table 1). A total of 540 and 823 patients were collected from the 1994 and 1999 databases, respectively, which represented 6.5% and 8.7% of the entire registry population, respectively. The 2004 cohort was characterized by a larger proportion of adenocarcinoma, more advanced age, less advanced clinical and pathologic T factors, and less pneumonectomy. In fact, the proportion of patients who underwent pneumonectomy in 2004 was almost half that of 1994. The R0 surgery rate tended to increase, but not to a statistically significant degree. Although statistical analysis could not be performed for "perioperative treatment" because adjuvant chemotherapy data were not collected until 1999, the proportion of patients who underwent induction treatment tended to increase.

Survival

The overall 5-year survival rate in the 2004 cohort was 30.1%, whereas that of 1994 and 1999 was 19.9% and 24.5%, respectively. When the survival curves were compared, the 2004 cohort was significantly better than the 1994 (p = 0.0001) and 1999 cohorts (p = 0.0411) (Fig. 1). The 5-year survival rates were 33.4% in 353 patients with R0 surgery, 21.7% in 24 patients with R1 surgery, and 0.0% in 51 patients with R2 surgery. The differences in survival between the R1 group and R2 groups and also between the R0 and R2 groups were statistically significant (p = 0.0098 and $p < 0.0001$, respectively), whereas no significant difference was found between the R0 and R1 groups (p = 0.6423) (Fig. 2*A*). The 5-year survival rate was for 27.5% for men was and 37.8% for women. The survival experience was significantly better for women than for men (p = 0.025) (Fig. 2*B*). As to the number of metastasized stations, there was a significant difference between single-station and multistation N2 patients (p = 0.0053) with the respective 5-year survival rates being 35.8% and 22.0% (Fig. 2*C*). Five-year survival rates were 28.1% in 105 patients who received induction treatment, 27.8% in 150 patients who received adjuvant chemotherapy, and 33.7% in 137 patients who underwent surgery alone.

DISCUSSION

Surgery is rarely indicated initially for c-stage IIIA-N2 NSCLC, because the disease is predisposed to possess serious local tumor burden and latent systemic disease. Surgery for cN2/pN2 resulted in a 5-year survival rate of approximately 10% 20 to 30 years ago[1,2] (Table 2). Reasons for this unfavorable prognosis included a high incidence of incomplete resection because of malignant pleurisy or extra nodal invasion, and of early recurrence in distant organs; 5-year survival was only 20% even in cases of complete resection.[3,4] Currently, many clinicians regard concurrent chemoradiotherapy as a standard care for resectable c-stage IIIA-N2 NSCLC, because a 20% 5-year survival rate has been achieved even for unresectable cases.[18,19] In our analysis of the 2004 nationwide registry, however, the outcome of 137 patients who underwent surgery alone showed 34% 5-year survival rate, which is more favorable in comparison with those of the early studies[1–4] or comparable to those of combined modalities[5–9] (Table 2). Although retrospectively analyzed, the present data are important as they reflect modern surgery results for cN2/pN2 NSCLC. One possible explanation for the above results is that selection of surgical candidate would have been sophisticated. The 2004 cohort was also characterized by less advanced T-parameter values and a smaller proportion of patients who underwent

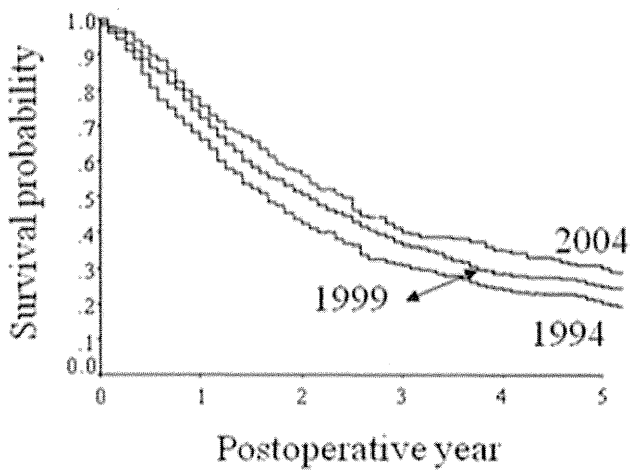

FIGURE 1. Survival curves for c-stage N2/pN2 non–small-cell lung cancer patients collected from the Japanese Lung Cancer Registry in 1994, 1999, and 2004. The postoperative 5-year survival rates of 554 patients in 1994, 823 patients in 1999, and 436 patients in 2004 were 19.9%, 24.5%, and 30.1%, respectively. Significant differences were observed between each series by log-rank test; p values were 0.0063 between 1994 and 1999, <0.0001 between 1994 and 2004, and 0.0411 between 1999 and 2004.