Trimodality Therapy for Lung Cancer With Chest Wall Invasion: Initial Results of a Phase II Study

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Background. The chest wall is the most common neighboring structure involved by locally advanced lung cancers. However, the optimal treatment strategy for such tumors has not been established. This phase II trial was therefore conducted with the aim of evaluating whether induction chemoradiotherapy followed by surgery improves the survival of patients with T3N0 or T3N1 lung cancer involving the chest wall.

Methods. Patients with resectable T3N0 or T3N1 non-small cell lung cancer involving the chest wall were candidates for this study. Induction therapy consisted of two cycles of cisplatin and vinorelbine chemotherapy concurrent with 40 Gy of radiation. Surgical resection was performed 3 to 6 weeks after the last day of chemotherapy.

Results. From January 2009 to November 2012, 51 eligible patients (40 stage IIB and 11 stage IIIA tumors) were entered in this study. Induction therapy was completed as planned in 49 (96%) patients, and 25 (51%) had a partial response revealed on computed tomography. Forty-eight patients underwent pulmonary resection combined with chest wall resection, and 44 (92%) underwent a complete resection. Pathologic examinations of the resected specimens revealed no viable tumor cells in 12 (25%) cases and minimal residual disease in 31 (65%) cases. Five patients experienced major postoperative complications, and 1 patient died of postoperative exacerbation of interstitial pneumonia.

Conclusions. The initial results of this study showed the treatment regimen to be safe and feasible with a high rate of a pathologic response for patients with lung cancer involving the chest wall in a multiinstitutional setting.

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The chest wall is the most common neighboring structure involved by lung cancers, and those locally advanced tumors are staged as T3 in the present TNM classification [1]. These T3 lung cancers 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; the 5-year survival of even N0 patients with non-small cell lung cancer (NSCLC) involving the chest wall has been reported to be 40% to 50% for more than one decade [2, 3]. Therefore, the optimal treatment strategy for such tumors should be established.

Induction therapy followed by surgery has become a standard strategy for superior sulcus tumors (SSTs), which can be described as lung cancer with apical chest wall invasion. There were two phase II studies of trimodality therapy for SST, which resulted in high rates of pathologic complete response and complete resection and better survival than previous reports [4, 5]. Based on the results of studies for SST, we supposed that induction therapy and surgery may also achieve the same high rate of a pathologic complete response in these patients, thereby improving the prognosis. Therefore, we

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conducted a phase II trial to test whether induction chemoradiotherapy using cisplatin and vinorelbine plus concurrent radiotherapy and surgical resection would improve the survival of patients with T3N0 or T3N1 NSCLC involving the chest wall.

Material and Methods

Study Design

A prospective phase II study (UMIN 000001810) was conducted by the Central Japan Lung Study Group, and 29 institutions were approved by means of each institutional review board (Appendix 1). Written informed consent was obtained from all participants before registration in this study. A schematic diagram of the study is shown in Figure 1. The primary end point of this study was the 3-year survival rate after the date of registration. The secondary end points were defined as the following: the completion and response rates of induction chemoradiation, the toxicity of induction therapy, the rate of resection or complete resection, the postoperative morbidity and mortality, the pathologic response, the recurrence rate, and the failure patterns. The method used for sample size calculations is described in Appendix 2.

Inclusion Criteria

Patients with histologically or cytologically proven NSCLC involving the chest wall were candidates for this study. The eligibility criteria included the following: no oncologic treatment before registration, age 20 to 70 years, Eastern Cooperative Oncology Group performance status of 0 or 1, predicted postoperative forced expiratory volume in 1 second of at least 0.8 L, and adequate organ functions. The staging modalities included contrast-enhanced computed tomography (CT) of the chest and upper abdomen, magnetic resonance imaging (MRI) or CT of the brain, and bone scintigraphy. The use of positron emission tomography was not mandatory. Based on a previous study [6], the clinical criteria for chest wall invasion were defined as follows: (1) findings of obvious tumor invasion into the soft tissue of the chest wall or ribs on CT, (2) findings of contiguity of the tumor and chest wall on CT with chest pain, or (3) findings of contiguity of the tumor and chest wall on CT with positive findings on bone scintigraphy.

Patients with SST, which was defined as that involving the first rib, were also included; however, those with T4 disease involving the subclavian vessels, brachial plexus, vertebra, or other organs were excluded from the study.

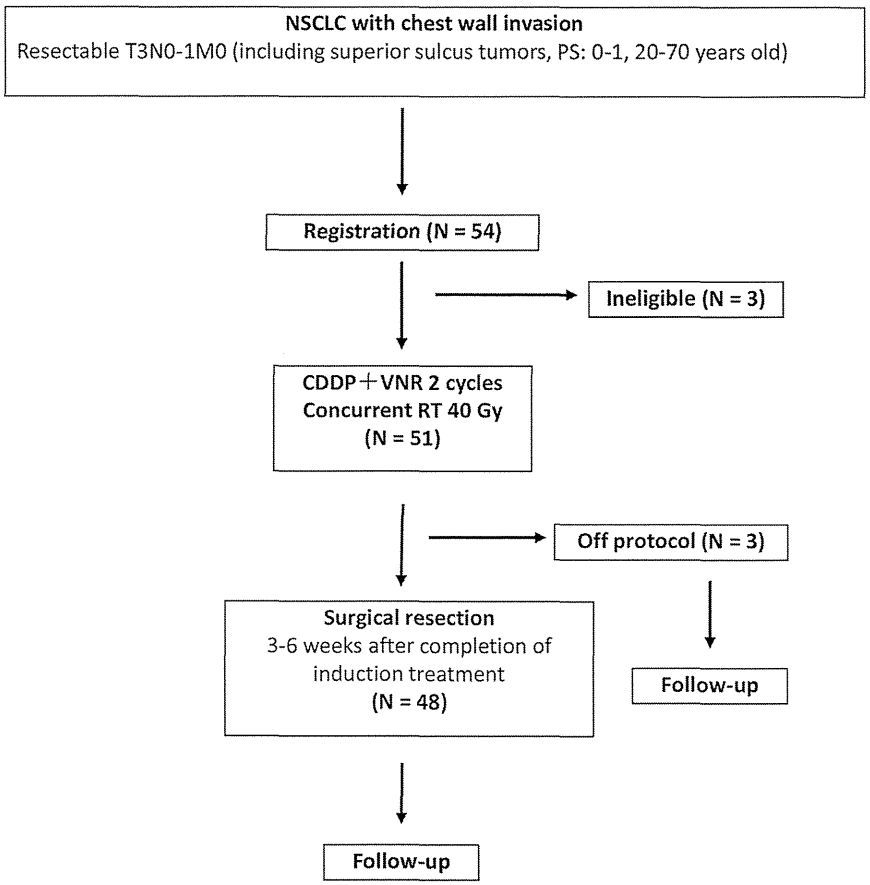

Fig 1. A schematic diagram depicting the Central Japan Lung Study Group (CJLSG) 0801. (CDDP = cisplatin; NSCLC = non-small cell lung cancer; PS = performance status; RT = radiation therapy; VNR = vinorelbine.)

Those with clinical N2 disease, which was diagnosed either radiographically or pathologically, were also ineligible.

Induction Therapy

The enrolled patients received two cycles of chemotherapy with a 4-week interval in between. Cisplatin was administered at a dose of 80 mg/m^2 on day 1, and vinorelbine was given at a dose of 20 mg/m^2 on days 1 and 8. The day 8 dose of vinorelbine or the second cycle of chemotherapy was canceled if any severe toxicity did not recover to grade 0 or 1 within the 2 weeks after day 8. The radiotherapy was started concurrently with the first day of chemotherapy, and was given at a total of 40 Gy in 20 fractions over 4 weeks. The radiation field was defined as the primary tumor; the mediastinal and hilar nodes were not irradiated. The toxicities were evaluated according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) ver. 3.0.

Surgical Resection, Pathology, and Boost Therapy

Every case was reassessed using physical examinations and contrast-enhanced CT of the chest and abdomen to judge the clinical response and resectability. The radiographic tumor response was judged according to the Response Evaluation Criteria in Solid Tumors [7]. After the determination made by the multidisciplinary team at each institution, surgical resection was performed 3 to 6 weeks after the completion of the induction therapy. A lobectomy or pneumonectomy combined with chest wall resection was required, in principle, with mediastinal lymph node dissection. The surgical approach, the method of reconstruction of the chest wall, and coverage of the bronchial stump were left to the discretion of the individual surgeon.

Information regarding the TNM classification was based on the 7th edition of the International Union Against Cancer-TNM staging system [1]. The pathologic response was divided into three categories: pathologic complete response (no residual microscopic tumors), minimal residual (viable cells detected in less than one third of the portion in the resected tumor), and other, based on the General Rule for Clinical and Pathological Record of Lung Cancer in Japan [8].

The protocol did not provide any limits to the use of boost therapy for patients who underwent incomplete resection or exploratory thoracotomy. For those with complete resection, only additional chemotherapy with the induction regimen was allowed, as decided by each institution.

Complications and Follow-Up

Although postoperative complications were checked separately without grading, severe complications were defined as follows: pneumonia, respiratory failure requiring ventilation, radiation pneumonia or fibrosis, a bronchopleural fistula, empyema, pulmonary embolism, postoperative bleeding requiring rethoracotomy, arrhythmia, chylothorax, prolonged air leakage, or others.

After the protocol treatment, the patients were followed up every 3 months during the first 3 years with physical examinations and chest roentgenograph and chest CT studies at 6-month intervals.

Statistical Analysis

The survival time was measured from the date of registration to the date of death or the last follow-up. Survival curves were estimated according to the Kaplan-Meier method, and differences in survival were assessed using the log-rank test. The data were analyzed using the SPSS 20.0 software program (SPSS, Inc, Chicago, IL).

Results

Patient Characteristics

From January 2009 to November 2012, 54 patients were enrolled in this study, 3 of whom were found to be ineligible. One patient was ineligible because the histologic diagnosis was altered to small cell lung cancer after starting the induction chemoradiotherapy. The second patient experienced dizziness after enrollment and was proven to have brain metastasis. The third was found to have progressive N2 disease on pretreatment CT, and received definitive concurrent chemoradiotherapy. Therefore, 51 patients were judged to be eligible, and the characteristics of these patients are presented in Table 1. There were 45 men and 6 women, with a mean age of 58 years. In terms of the tumor histology, adenocarcinoma was the most common, followed by squamous cell carcinoma.

Forty-five (88%) patients complained of chest pain before the induction therapy, and 33 of them had findings of obvious tumor invasion into the soft tissue of the

Table 1. Characteristics of Eligible Patients (n = 51)

Characteristic	Number of Patients	%
Mean age, years (range)	58 (30–69)	
Sex		
Male	45	88
Female	6	12
Histology		
Adenocarcinoma	26	51
Squamous cell carcinoma	15	29
Other	10	20
Diagnosis of chest wall invasion		
Obvious tumor invasion into the soft tissue of the chest wall or ribs	39	76
Contiguity of the tumor and chest wall with chest pain	12	24
Contiguity of the tumor and chest wall with positive findings on bone scintigraphy	0	0
Clinical stage		
T3N0M0	40	78
T3N1M0	11	22

chest wall or ribs on CT. The other 6 patients had no chest pain, although the CT of each patient showed obvious tumor invasion into the soft tissue or ribs. Bone scintigraphy was performed on 26 patients, and hot lesions neighboring the tumor were detected in 11 patients, who also had definitive positive findings of chest wall invasion on CT. The mean tumor size in maximum diameter before the treatments was 5.4 cm, ranging from 3.0 to 9.0 cm. Concerning the N status, 48 patients were staged by positron emission tomography and CT, and 3 patients were staged as N0 by histologic examinations including mediastinoscopy, endobronchial ultrasonography, or video-assisted thoracoscopic surgery.

Induction Therapy

Induction therapy was completed as planned in 49 (96%) patients, with no treatment-related death. All patients could finish the radiotherapy, whereas 2 patients received only one cycle of chemotherapy owing to the development of adverse events. The major toxicities of the induction chemoradiotherapy are listed in Table 2. Based on the CTCAE grade, 41% of patients had grade 0 to 2 toxicities, 43% had grade 3 toxicities, and 16% had grade 4 toxicities. Leukopenia and neutropenia were the most common toxicities, whereas only 1 patient experienced grade 3 anemia and needed a transfusion. A pulmonary embolism occurred in 2 patients, and duodenal ulcer perforation occurred in 1; however, these patients continued to participate in the study and received curative resections within the defined term.

Progressive disease developed in 1 patient after the induction therapy. Twenty-six (51%) patients had a partial response revealed on CT, whereas none of the patients exhibited a complete response.

Surgical and Pathologic Results

Forty-eight patients underwent pulmonary resection combined with chest wall resection (Table 3). Lobectomy was performed in all but 1 patient, who underwent a wedge resection of the right upper lobe of the lung combined with resection of the subclavian artery. The number of resected ribs ranged from one to five, with a mean of 2.8, and 7 patients underwent extrapleural resection without removing any ribs. Six patients underwent combined resection with a part of the vertebral body or transverse process, although their tumors were diagnosed pathologically as T3 without spinal invasion. The median estimated blood loss was 402 mL (range, 23 to 3,622 mL), and 12 patients received a transfusion during the surgery. Table 4 presents the major complications after the surgical treatment. One patient underwent a reoperation because of bleeding, and after a while, experienced exacerbation of interstitial pneumonia that required respiratory support. A bronchopleural fistula, followed by empyema, developed sequentially, and he died 6 months after the first operation. The mortality rate was therefore 2%.

Table 2. Major Toxicities of Induction Therapy

Toxicities	Grade 3	Grade 4	% of Patients With Grade 3/4
Leukopenia	16	3	37
Neutropenia	16	6	43
Anemia	1	0	2
Anorexia	8	0	16
Nausea	7	0	14
Diarrhea	1	0	2
Infection	3	0	6
Pulmonary embolism	1	1	4
Perforation of a DU	0	1	2

DU = duodenal ulcer.

Table 3. Surgical Results of Eligible Patients (n = 48)

Factors	No. of Patients	%
Surgical procedure		
Lobectomy	47	98
Wedge resection	1	2
Combined resection		
Parietal pleura	48	100
Chest wall (any ribs)	41	85
First rib	16	33
Vertebra	6	13
Subclavian artery	1	2

Based on the pathologic results, 44 (92%) of the patients underwent a complete resection (Table 5). The pathologic examinations of the resected specimens revealed no viable tumor cells in 12 (25%) cases and minimal residual disease in 31 (65%) cases. Downstaging of the tumor compared with the clinical stage observed before induction therapy was identified in 21 patients after surgery, whereas progressive disease was proven in 5 patients; T4 in 1 patient, N2 in 2 patients, and M1b of metastasis to the rib or to extrathoracic lymph nodes in 2 patients. Seven patients who underwent extrapleural dissection were confirmed to have a negative margin at the chest wall site.

Boost Therapy

One or two cycles of adjuvant chemotherapy consisting of the same regimen as was used in the induction therapy was administered to 7 patients. Two of the

Table 4. Major Complications After the Surgical Treatment

Factors	No. of Patients	%
Empyema	2	4
Exacerbation of IP	2	4
Bleeding	2	4
Pneumonia	1	2
Bronchopleural fistula	1	2
Chylothorax	1	2

IP = interstitial pneumonia.

Some patients had more than one complication.

Table 5. Pathologic Findings of the 48 Patients Who Underwent Surgery

Factors	No. of Patients	%
Completeness		
R0	44	92
R1	3	6
R2	1	2
Pathologic response		
Complete	12	25
Minimal residual[a]	31	65
Other	5	10
Pathologic stage		
T0N0M0	12	25
T1–2N0M0	7	15
T3–4N0M0	22	46
TxN1–2M0	5	10
TxNxM1	2	4
Downstaged	21	44

[a] Minimal residual is defined as less than one third of viable cells detected in the resected specimen.

4 patients who underwent incomplete resection received adjuvant chemotherapy, and another patient received additional radiation to the surrounding tissue of the right subclavian artery, where a microscopic residual tumor was proven by the pathologic examination. The remaining patient did not receive any adjuvant therapy owing to major complications after surgery.

Recurrence and Survival

At a median follow-up period of 16 months, 12 of the 48 patients who completed the protocol had recurrence of the disease. The failure pattern included 5 cases of local relapse and 7 cases of distant metastasis, with the brain being the most common site of recurrence in 3 patients. The overall and progression-free survival curves are shown in Figure 2. Five patients died of the disease, 1 of whom had a progressive response (bone metastasis) to the induction chemoradiotherapy and did not undergo surgery. Two patients with only one cycle of chemotherapy because of the adverse events underwent complete surgical resection and were alive for more than 15 months without recurrence. The 2-year overall and progression-free survival rates were 85% and 71%, respectively.

Although the follow-up period is relatively short, there have been no deaths from the disease in the 21 patients with downstaged disease, except for the postoperative mortality case. The overall survival curves of the patients stratified by their response to the induction chemoradiotherapy are presented in Figure 3.

Comment

Lung cancer with chest wall invasion is still common, and is considered to be a potentially curable disease, except for cases with N2 disease or distant metastasis [2]. However, the surgical results for these locally advanced tumors have not been developed for more than one decade [2, 3]. The optimal treatment strategy for such tumors has not been established, although adjuvant chemotherapy is recommended for patients with completely resected stage II and IIIA NSCLC in the guidelines of the American College of Chest Physicians and the National Comprehensive Cancer Network [9–11]. The JBR.10 and ANITA trials showed the improvement of survival with the use of adjuvant chemotherapy using a combination of cisplatin and vinorelbine for these patients; however, there were little data available about how many cases of lung cancer with chest wall invasion were included in these studies [12, 13]. The recent

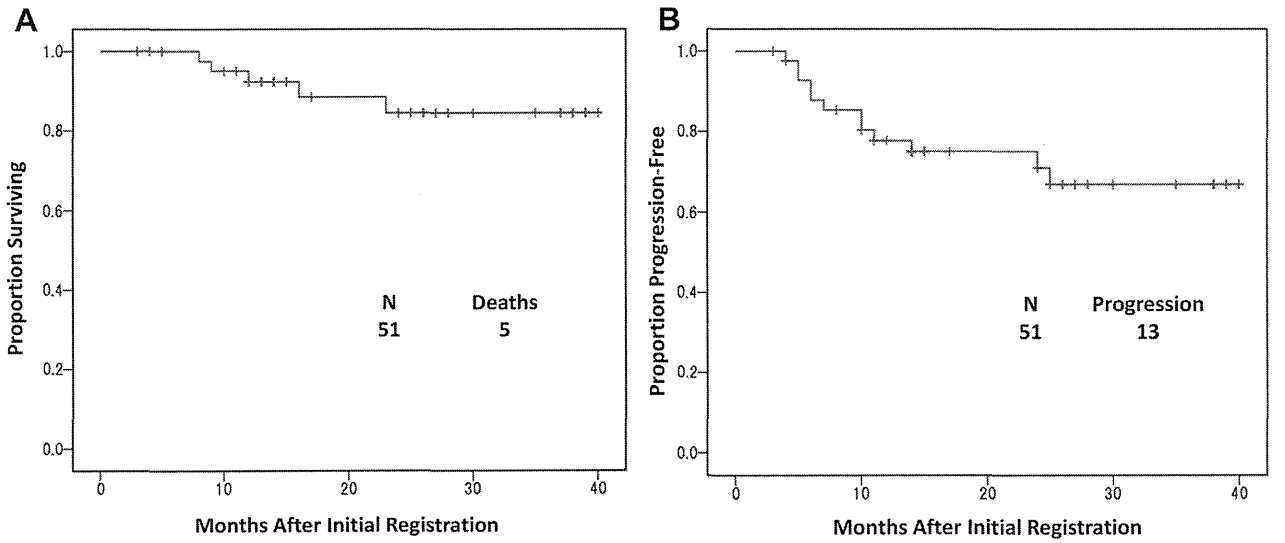

Fig 2. The (A) overall and (B) progression-free survival curves from the day of the registration. The 2-year overall and progression-free survival rates were 85% and 71%, respectively.

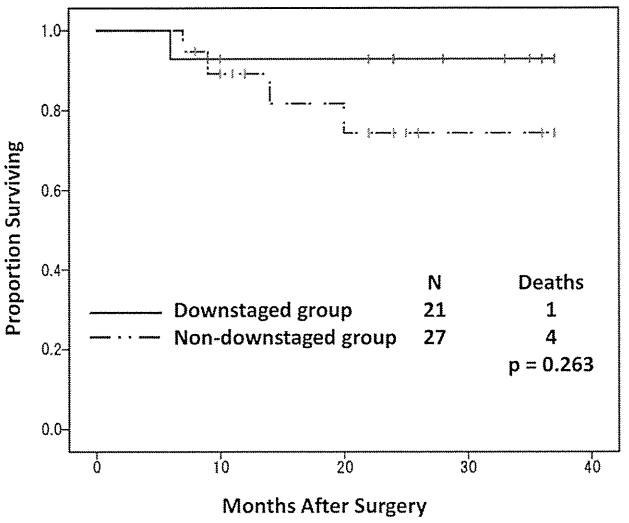

Fig 3. The overall survival curves of patients stratified by their response to the induction chemoradiotherapy. No significant difference was seen between the two groups ($p = 0.263$), although patients with downstaged disease (solid line) seemed to have better survival than those who did not have downstaged disease (dashed line).

research reported by the Japanese Joint Committee of Lung Cancer Registry in 2010 also indicated the effectiveness of adjuvant chemotherapy for patients with T3 disease, although only one third of T3 patients who underwent surgical treatment received adjuvant chemotherapy, and detailed information, such as the chemotherapy regimen or dose intensity, was not collected in the registry [3]. Therefore, whether the same strategy is appropriate for both patients with such locally advanced lung cancer and those with lymphatic metastases is unclear.

On the other hand, SSTs have been treated using induction radiation and surgery since the strategy was reported by Shaw and colleagues in 1961 [14]. Because of the difficulty of the surgical approach and the limited potential for complete resection because of the anatomic considerations, induction therapy had been spotlighted for SSTs, and two multiinstitutional phase II studies of induction chemoradiation followed by surgery were conducted in the United States and Japan, both of which revealed high rates of complete resection and better survival than the previous literature [4, 5]. On the other hand, the rate of complete resection for lung cancer with chest wall invasion is relatively high; approximately 12% of patients with these diseases undergo incomplete resection based on the Japanese registry database [3]. Meanwhile, we presumed that the tumors were likely to acquire vascular feeding arteries from the chest wall and that induction chemoradiation would therefore be more effective in these patients than in those with N2 disease. Hence, this phase II study was conducted with the aim of improving the survival of lung cancer patients with chest wall invasion, not only by increasing the rate of resectability, but also by improving the ability to achieve a pathologic complete response, controlling micrometastases, securing time to assess the surgical curability, and so on. In fact, 2 patients registered in this study were proven to have progressive N2 disease or brain metastasis during the initial term of induction therapy, and noncurative surgical treatment was avoided.

In addition, the regimens used when performing chemotherapy for lung cancer have advanced in recent years. The two phase II studies of SST mentioned above included the classical regimens of cisplatin plus etoposide or cisplatin plus vindesine plus mitomycin. On the other hand, the efficacy of cisplatin and vinorelbine, a third-generation agent, plus concurrent radiotherapy, was tested in a phase I study with acceptable side effects [15], and a better response rate was reported among patients with inoperable stage III NSCLC [16]. Therefore, we decided to adopt this modern regimen for the present study.

Induction chemoradiotherapy followed by surgery was proven to be safe and acceptable in this study; there were no cases of 30-day mortality and few major complications. One reason for this finding may be the dose of radiation. Although the two studies of SST adopted a dose of 45 Gy in 25 fractions and showed excellent effects, the radiologists at our institutions achieved a similar effect with a dose between 40 Gy in 20 fractions and 45 Gy in 25 fractions based on the concept of a biologically effective dose. A couple of studies have advocated that high-dose radiotherapy as part of the trimodality treatment for SST was beneficial [17, 18]; however, these tumors were sometimes adjacent to the vertebra, and a limited dose of radiation to the spinal cord was usually defined to be within 50 Gy. In addition, these types of surgeries sometimes require the combined resection of great vessels with vascular reconstruction, and the safety and efficacy of such treatments after high-dose radiotherapy still remain controversial. Although the complete response rates of the two studies including high-dose radiation were 53% and 41%, which were higher than the 25% in this study, we believe that our less toxic regimen would compensate for the inferiority of the pathologic complete response rate in terms of the prognosis of the patients, especially in the multiinstitutional setting.

There were several limitations associated with this study. First, there is a possibility of inaccurate clinical staging of the tumors. Because invasive assessments of the lymph nodes and positron emission tomography were not mandatory, N2 disease and distant metastasis may have been inaccurately diagnosed before the initiation of induction therapy. However, only 2 patients, each with mediastinal nodal metastasis and a distant tumor, were identified before surgery. Second, we did not restrict the institutions that participated in this study; therefore, the patient selection, surgical technique, and other factors in each institution might not be uniform. Third, the inclusion criteria regarding the age of patients in this study was decided to have a cutoff of 70 years because of the multiinstitutional setting, although the peak age of patients who were diagnosed with lung cancer was approximately 70 years old. Moreover,

although the majority of patients included in this study were male, this polarization factor is general based on the Japanese registry database [3].

In conclusion, the trimodality treatment comprising induction chemoradiotherapy followed by surgery for patients with resectable T3N0 or T3N1 NSCLC involving the chest wall was proven to be safe and feasible in a multiinstitutional setting. Whether this treatment strategy is effective in improving the prognoses of these patients will be determined after 3 years.

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DISCUSSION

DR JACK A. ROTH (Houston, TX): One of the problems with administering radiation preoperatively is that additional large doses of radiation cannot be given postoperatively if the margins are positive. How did you treat those patients who had R1 and R2 resections?

DR KAWAGUCHI: Pardon me.

DR ROTH: How did you treat the patients who had residual cancer after surgery since you could not give any further radiation therapy?

DR KAWAGUCHI: Three patients had positive margins where minimal residual tumor was proven at the chest wall and bronchial stump. Another patient was judged as R2 resection because of distant metastasis to a rib, which was excised during the surgery.

DR THOMAS K. VARGHESE JR. (Seattle, WA): Did you do any further treatment for that?

DR KAWAGUCHI: One patient had radiation therapy to the surrounding tissue of the right subclavian artery, where a microscopic residual tumor was proven by the pathological examination. Another 2 patients who had distant metastasis to a rib or microscopic residual tumor at the chest wall received adjuvant chemotherapy, and the last one did not have any adjuvant therapy due to major complications after surgery.

DR ROTH: Well, again, you cannot give a really significant dose of postoperative radiation after you have given 40 Gy preoperatively, so I just wondered how effective that was.

DR MATTHEW G. BLUM (Colorado Springs, CO): Following up on that a little bit, outside of spinal radiation or brachial plexus radiation, why wouldn't you go with higher doses? You are going to remove that portion of the chest wall anyway. I'm not quite sure why you wouldn't go with a higher dose to start with so that you just give everything you can there.

The second question, if I understood that correctly, there was no hilar or mediastinal radiation. This was just to the primary tumor?

DR KAWAGUCHI: The second question is about the irradiated area?

DR BLUM: Yes. You just gave the radiation to the primary tumor without any nodal bed radiation at all?

DR KAWAGUCHI: Only the primary site; no hilar or mediastinal radiation, because we considered that tumors with chest wall invasion are peripheral, and many times N2 lymph nodes are not involved.

DR BLUM: And why wouldn't you use higher doses, say, to 65 Gy instead of 40?

DR KAWAGUCHI: The dose of radiation is controversial. The Intergroup trial of SST (superior sulcus tumor) adopted a dose of 45 Gy in 25 fractions and showed excellent effects. Although the total dose used in the present study was slightly smaller, the radiologists at our institutions revealed a similar effect with a dose between 40 Gy in 20 fractions and 45 Gy in 25 fractions based on the concept of a biologically effective dose. Concerning the high dose of radiation, these tumors are sometimes adjacent to the vertebra, and a limited dose of radiation to the spinal cord is usually defined to be within 50 Gy. So we adopted a dose of 40 Gy in the multiinstitutional setting.

DR ERIC VALLIERES (Seattle, WA): Thank you for this nice study.

I noticed that you had 7 patients who only had an extrapleural approach without chest wall resection. To decide that an extrapleural resection suffices is one of the hardest decisions to make in someone with a nonirradiated chest that appears to have parietal involvement. How did these 7 patients in whom you only went extrapleural do—what was their survival?

DR KAWAGUCHI: That is a very important point. Seven patients had only extrapleural resection without removing the ribs, and they were confirmed to have a pathologically negative margin at the chest wall site. Based on the preoperative CT (computed tomography) findings, we cannot be certain whether the tumor invaded only the parietal pleura prior to the induction therapies.

DR VALLIERES: How did you make those decisions intraoperatively during surgery?

DR KAWAGUCHI: During surgery?

DR VARGHESE: While you were in surgery, how did you make the decision to go extrapleural?

DR KAWAGUCHI: Extrapleural?

DR VARGHESE: You had 7 patients with the extrapleural approach.

DR KAWAGUCHI: Yes.

DR VARGHESE: How did you make that decision?

DR KAWAGUCHI: During the thoracotomy? Not by preoperative CT findings?

DR VARGHESE: Yes, during the thoracotomy. How did you make that decision?

DR KAWAGUCHI: This study is a multiinstitutional setting, so its decision was each surgeon's decision. However, we consider that an experienced surgeon could accurately assess whether an extrapleural or en-bloc resection was appropriate to achieve a complete resection during an operation. In fact, only 2 patients had incomplete resection owing to the site of dissected chest wall.

DR NASSER K. ALTORKI (New York, NY): The way I interpret the data is that the only patients that benefited from this are only the 7 patients. One objective in giving induction therapy to patients with chest wall invasion is perhaps to do a lesser resection, or not at all, but you did a chest wall resection in 41, so what is the benefit of this regimen in your view?

DR KAWAGUCHI: The complete resection rate was considerably high, up to 92%, which may be due to the favor of induction therapy. In addition, 25% of patients had pathological complete response and 65% had minimal residual disease. Therefore, we expect for long-term survivals in the study cohort.

Concerning 7 patients only with extrapleural resection, although the tumor invasion was limited to the parietal pleura, whether it was due to the induction therapy or not was unknown.

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ORIGINAL ARTICLE – THORACIC

Therapeutic surgery without a definitive diagnosis can be an option in selected patients with suspected lung cancer

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Abstract

OBJECTIVES: With the recent improvements in the diagnostic accuracy of radiographic modalities, it might be an option to perform therapeutic surgery without a definitive diagnosis for selected patients with suspected lung cancer based on the findings of diagnostic imaging.

METHODS: Between April 2008 and December 2012, all nodules without a definitive diagnosis were classified into five categories according to the probability of lung cancer based on the diagnostic imaging: Category 1 (Benign), Category 2 (Probably benign), Category 3 (Intermediate), Category 4 (Suspected malignancy) and Category 5 (Highly suggestive of malignancy). In this study, the 232 surgical candidates for suspected clinical stage I lung cancer without a preoperative definitive diagnosis were considered to be Category 3 ($n = 29$), Category 4 ($n = 46$) and Category 5 ($n = 157$). Eighty-two patients (72% of Category 3, 46% of Category 4 and 25% of Category 5) had an intraoperative diagnosis during surgery, whereas the remaining 150 patients did not. The final pathological diagnosis and surgical outcomes were analysed.

RESULTS: The final pathological diagnosis of the 232 suspicious nodules revealed 214 lung cancers (52% of Category 3, 93% of Category 4 and 99% of Category 5). Wedge resection was performed for all seven benign tumours. In the multiple regression analysis, intraoperative diagnosis was a significant factor for the length of the operation. In the multivariate logistic regression analysis, the length of the operation was a significant factor predicting both the postoperative morbidity and a prolonged hospital stay.

CONCLUSIONS: Based on a careful clinical decision made using the current diagnostic imaging strategies, patients with a high probability of lung cancer are good candidates for therapeutic surgery, even without a preoperative or intraoperative definitive diagnosis.

Keywords: Lung cancer • Diagnosis • Surgery • Frozen section

INTRODUCTION

Lung cancer is now one of the most common malignancies causing death worldwide. Lobectomy with systematic mediastinal lymph node dissection has been the most effective therapeutic surgery for patients with early-stage lung cancer [1–3]. Additionally, although the results of two ongoing randomized trials are still forthcoming, segmentectomy is becoming a valid alternative therapeutic surgery for selected patients with limited pulmonary function or with peripheral nodules ≤2 cm in diameter [3–5]. To date, obtaining a definitive histological or cytological confirmation before therapeutic surgery has been the gold standard in patients with suspected lung cancer, to help avoid unnecessary lobectomy for benign tumours. In the American College of Chest Physicians guidelines, a surgical diagnosis is considered when the clinical probability estimate of malignancy is high (>65%) and a fully informed patient prefers to undergo a definitive diagnostic procedure [6]. In the National Comprehensive Cancer Network guidelines, a biopsy before surgery is not required for patients with a strong clinical suspicion of lung cancer; however, an intraoperative diagnosis, such as a pathological consultation with wedge resection or needle biopsy, is considered to be necessary before lobectomy [7].

The introduction of new radiographic modalities, such as thin-section computed tomography (CT) and positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) combined with CT, has improved the diagnostic accuracy for distinguishing lung cancer from benign tumours [8]. In selected patients with highly suspected lung cancer based on the findings of diagnostic imaging, these improvements could reduce the risk of oversurgery, such as unnecessary lobectomy for a benign tumour following a missed radiographic diagnosis. It might be an optional treatment for such patients to perform therapeutic surgery without a definitive pathological diagnosis before or during surgery, resulting in a reduction

in the time and costs due to diagnostic procedures. This study was designed to elucidate the risks and benefits of performing therapeutic surgery without a definitive diagnosis for patients with suspected lung cancer on diagnostic imaging and, consequently, to consider whether two aims can be achieved: avoiding oversurgery and saving time and costs.

MATERIALS AND METHODS

This study was conducted with the approval of the Institutional Review Board of Nagoya University Hospital. We reviewed the medical records of 491 consecutive patients who underwent pulmonary resection for known or suspected clinical stage I lung cancer at Nagoya University Hospital between April 2008 and December 2012. Two hundred and two patients who had a preoperative pathological diagnosis before presentation to our department, six patients with R2 resection, two patients who underwent concomitant cancer resection of the lung and other organs, two patients who underwent concomitant cardiovascular surgery and seven patients with incomplete data on pulmonary function tests, were excluded from the analysis. Forty patients with nonsolid nodules were also excluded because of the poor agreement of the significant morphological differentiators between atypical adenomatous hyperplasia (AAH), adenocarcinoma *in situ* (AIS: formerly bronchioloalveolar carcinoma) and invasive adenocarcinoma [9]. Consequently, 232 patients who did not have a preoperative definitive diagnosis constituted the study population (Fig. 1).

During the study period, all nodules without a definitive diagnosis were classified into five categories according to the probability of lung cancer estimated by one chest radiologist (Shingo Iwano) with over 15 years of experience reading thoracic CTs based on the clinical records and radiographic findings on CT and PET-CT scans: Category 1 (Benign), Category 2 (Probably benign), Category 3 (Intermediate), Category 4 (Suspected malignancy) and Category 5 (Highly suggestive of malignancy: with at least 95% chance of being cancer).

Figure 2 shows the algorithmic approach used for the probability estimate of lung cancer. The nodules were primarily classified based on the nodule type and the proven significant differential findings, such as spicula, pleural retraction and nodule size on CT, contrast enhancement and maximum standardized uptake value (SUVmax) on PET-CT. The nodules with calcification were classified into Category 1 or 2. The classification was comprehensively determined on revision with the clinical records and the other findings, such as tumour doubling time, bubble-like lucency, air bronchogram, vascular convergence, central cavity, satellite lesion, hilar and mediastinal lymph node swelling, etc. [8–13]. The findings on CT and PET-CT scans performed outside our institution were also considered for the classification. The surgical candidates in the current study were considered to be Category 3 ($n = 29$), Category 4 ($n = 46$) and Category 5 ($n = 157$).

Table 1 summarizes the characteristics of 80 part-solid nodules and 152 solid nodules stratified by the probability of lung cancer based on the diagnostic imaging findings. Preoperative biopsy was performed in 99 of 232 nodules, but all nodules remained without a definitive lung cancer diagnosis.

Considering this classification, the accessibility for wedge resection or needle biopsy, the surgical risk and the risk estimate of oversurgery without an intraoperative pathological confirmation, it was decided whether to obtain an intraoperative diagnosis of the primary nodule at the institutional preoperative conference comprising thoracic surgeons (Fig. 3A–D). As for Category 3, an intraoperative diagnosis was usually obtained. However, sublobar resection was performed without a definitive diagnosis in patients with small nodules and a poor surgical risk for lobectomy. As for Category 4, whether to obtain an intraoperative diagnosis was comprehensively decided based on the accessibility for wedge resection or needle biopsy, age, nodule size and surgical risk. As for Category 5, although an intraoperative diagnosis was most often not required, a part of cases with a small nodule in the peripheral lung field had an intraoperative diagnosis. A preoperative or intraoperative diagnosis was obtained before therapeutic surgery when the patient indicated a preference for this option in the preoperative interview.

Wedge resection and segmentectomy, instead of lobectomy, were performed in selected patients with previous pulmonary resection, limited pulmonary function, another major comorbidity or with peripheral nodules ≤2 cm in diameter. Systematic lymph node dissection was generally performed in cases with segmentectomy and lobectomy. However, it was not performed in older patients or with poor surgical risk. An intraoperative diagnosis of the resected specimen was used to determine whether to perform systematic lymph node dissection in some cases.

The correlations between the presence of a preoperative or intraoperative definitive diagnosis, the final pathological diagnosis, the surgical procedure, the length of the operation, postoperative morbidity and a prolonged hospital stay were analysed.

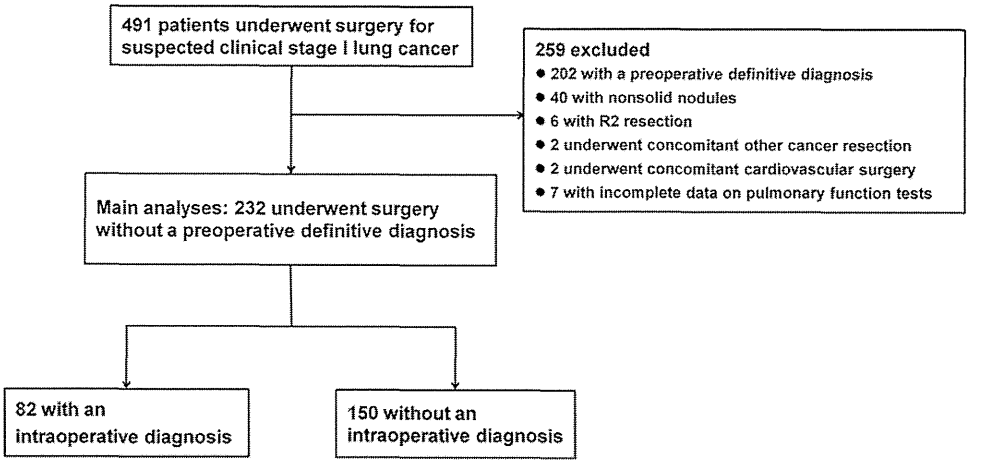

Figure 1: The study profile.

ORIGINAL ARTICLE

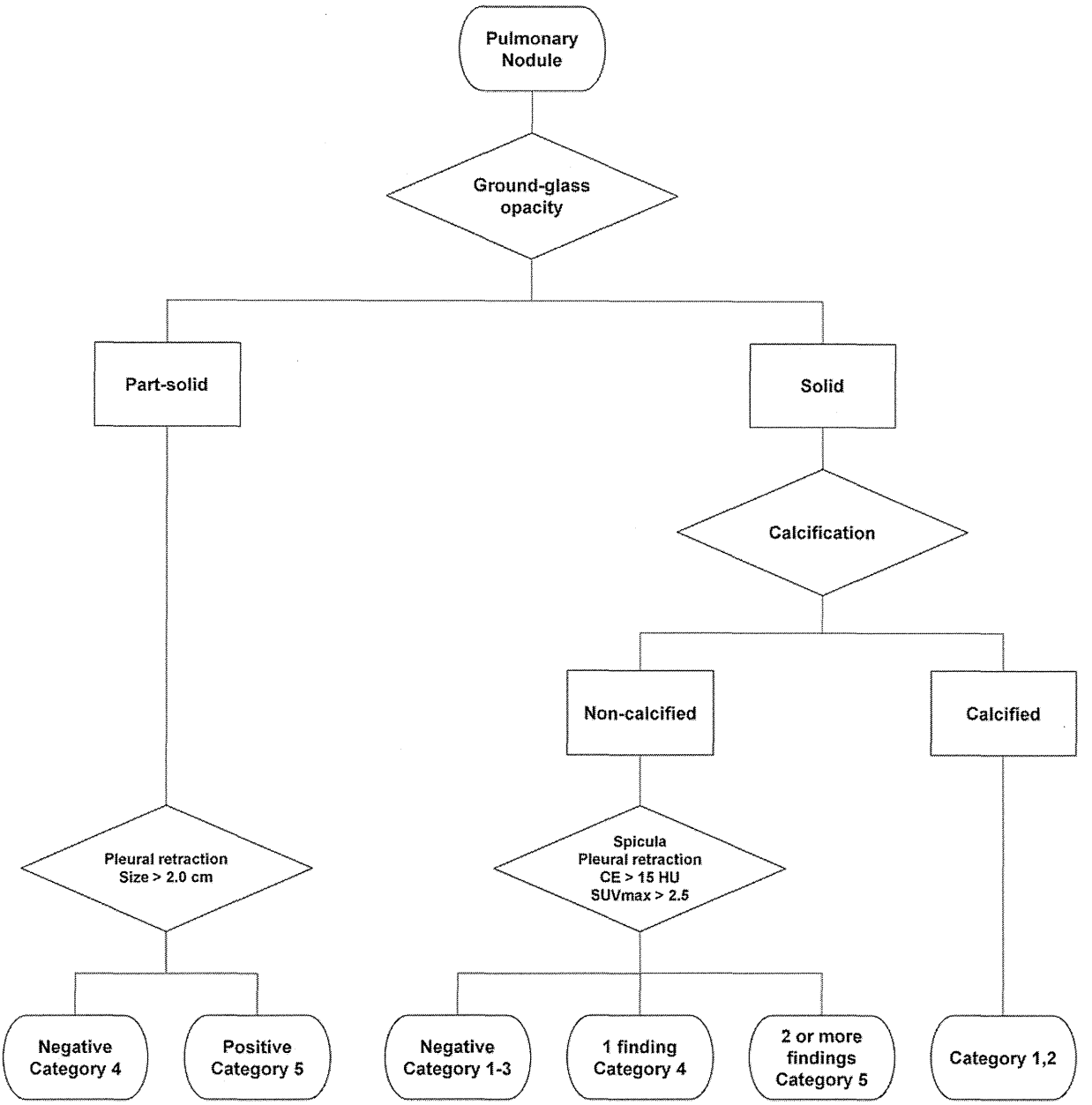

Figure 2 : The algorithmic approach used for the probability estimate of lung cancer.

CT scans were performed with a 64-channel multidetector-row CT scanner (Aquilion64: Toshiba Medical Systems, Tokyo, Japan) in the craniocaudal direction with inspiratory apnoea. The reconstruction thickness was 0.5–1 mm using a high spatial frequency algorithm for lung window settings and a standard algorithm for mediastinal window settings. For vessel and tumour enhancement, 96 ml of non-ionic contrast medium was used at a flow rate of 3.0 ml/s. PET scans were performed with a PET-CT scanner (Biography 16; Siemens Medical Solutions, Erlangen, Germany). Patients were required to fast for at least 6 h before imaging. The FDG dose was 3.7 MBq/kg (body weight <60 kg) or 4.07 MBq/kg (body weight ≥60 kg). Fifty minutes after the intravenous injection of FDG, emission scans of the area between the proximal femora and the base of the skull were acquired. The maximum value in a region of interest around the pulmonary lesion was defined as the SUVmax.

The 7th edition of the tumour-node-metastasis classification [14] was applied in this cohort, and the pathological diagnosis of the tumour was made based on the World Health Organization classification [15]. AIS was considered to be lung cancer, whereas AAH was considered to be a benign tumour. Postoperative morbidity was defined as the occurrence of at least one postoperative event based on The Society of Thoracic Surgeons General Thoracic Surgery Database [16]. A prolonged hospital stay was defined as hospitalization longer than 14 days postoperatively.

Statistical analysis

The chi-square and Kruskal-Wallis tests were used for comparisons of proportions and continuous values, respectively. The multivariate logistic regression analysis was performed to estimate

Table 1: The characteristics of 80 part-solid nodules and 152 solid nodules stratified by the probability of lung cancer based on the diagnostic imaging

Probability category	Part-solid				Solid			
	Category 3	Category 4	Category 5	*P*-value	Category 3	Category 4	Category 5	*P*-value
Number	0	10	70		29	36	87	
Age [(mean ± SD), years]	-	72.2 ± 5.2	68.3 ± 8.2	0.1532	68.6 ± 6.2	69.9 ± 9.0	68.2 ± 9.1	0.4563
Sex								
Female	-	2	39	0.0298	9	7	28	0.3322
Male	-	8	31		20	29	59	
Smoking status								
Never	-	3	41	0.0879	11	5	22	0.0800
Current or former	-	7	29		18	31	65	
Nodule size [(mean ± SD), cm]	-	1.7 ± 0.8	2.6 ± 0.9	0.0042	1.8 ± 0.8	2.2 ± 1.1	2.2 ± 0.9	0.1491
Contrast enhancement								
Negative (≤15 HU)	-	-	-	-	10	5	7	0.0003
Positive (>15 HU)	-	-	-	-	10	27	73	
NA	-	-	-	-	9	4	7	
SUVmax								
Negative (≤2.5)	-	7	48	0.0757	16	8	21	0.0018
Positive (>2.5)	-	0	13		10	28	61	
NA	-	3	9		3	0	5	
Spicula or pleural retraction								
Negative	-	9	35	0.0104	20	26	35	0.0008
Positive	-	1	35		9	10	52	
Preoperative biopsy								
Non-diagnostic results	-	3	21	1.000	9	19	47	0.0851
Not performed	-	7	49		20	17	40	
Pathological diagnosis								
Lung cancer	-	10	70	-	15	33	86	<0.0001
Other malignant tumours	-	0	0		9	2	0	
Benign	-	0	0		5	1	1	
Diagnostic accuracy for lung cancer (%)	-	100	100		52	92	99	

SUVmax: maximum standardized uptake value; SD: standard deviation; HU: Hounsfield units; NA: not available.

the odds ratios and 95% confidence intervals for postoperative morbidity and a prolonged hospital stay. The multiple regression analysis was performed to estimate the relative changes in the clinicosurgical parameters for the length of the operation. Statistical significance was defined as $P < 0.05$. All analyses were conducted using the JMP software program (version 8.0.1, SAS Institute, Inc., Cary, NC, USA).

RESULTS

The clinicopathological characteristics of patients are presented in Table 2. The mean age was 68.7 years. Eighty-five patients were female and 147 patients were male. Eighty-two patients, including 72% of Category 3, 46% of Category 4 and 25% of Category 5, obtained an intraoperative diagnosis before the therapeutic surgery was performed, and 150 patients did not. The sensitivity and specificity of an intraoperative diagnosis of malignancy were 95 and 100%, respectively (false negative in four nodules). Wedge resection in 29 patients, segmentectomy in 45 and lobectomy in 158 were performed. The final pathological diagnosis of the 232 tumours revealed 214 lung cancers (52% of Category 3, 93% of Category 4 and 99% of Category 5), 11 other malignant tumours (31% of Category 3, 4% of Category 4 and 0% of Category 5) and seven benign tumours (17% of Category 3, 2% of Category 4 and 1% of Category 5). All 80 part-solid-type nodules were found to be lung cancer with adenocarcinoma histology.

In 29 nodules classified into Category 3, five (17%) nodules were benign. In 203 nodules classified into Categories 4 and 5, only two (1%) nodules were benign, and 201 (99%) nodules were lung cancer and other malignancies (Fig. 3D). Wedge resection was performed in all seven patients with benign tumours.

Of the 214 lung cancers, 197 tumours were classified as pathological stage 0 or I disease, ten were classified as pathological stage II disease and seven were classified as pathological stage III disease. One hundred and sixty-seven tumours were adenocarcinomas, 30 were squamous cell carcinomas and 17 were of other histological types. The 30-day postoperative mortality rate was 0%, the postoperative morbidity rate was 23% and a prolonged hospital stay (>14 days) was noted for 8% of the patients.

The mean lengths of the operations in patients without an intraoperative diagnosis (wedge resection: 85.8 min; segmentectomy: 177.1 min; lobectomy: 179.2 min) were shorter than those in patients with an intraoperative diagnosis (wedge resection: 105.3 min; segmentectomy: 205.7 min; lobectomy: 212.3 min). In the multiple regression analysis for the length of the operation, age, segmentectomy, lobectomy and intraoperative diagnosis were identified to be significant factors ($P = 0.0251$, <0.0001, <0.0001 and 0.0013, respectively), whereas sex, smoking status, nodule size, predicted postoperative (ppo) forced expiratory volume in the first second, ppo diffusing capacity of the lung for carbon

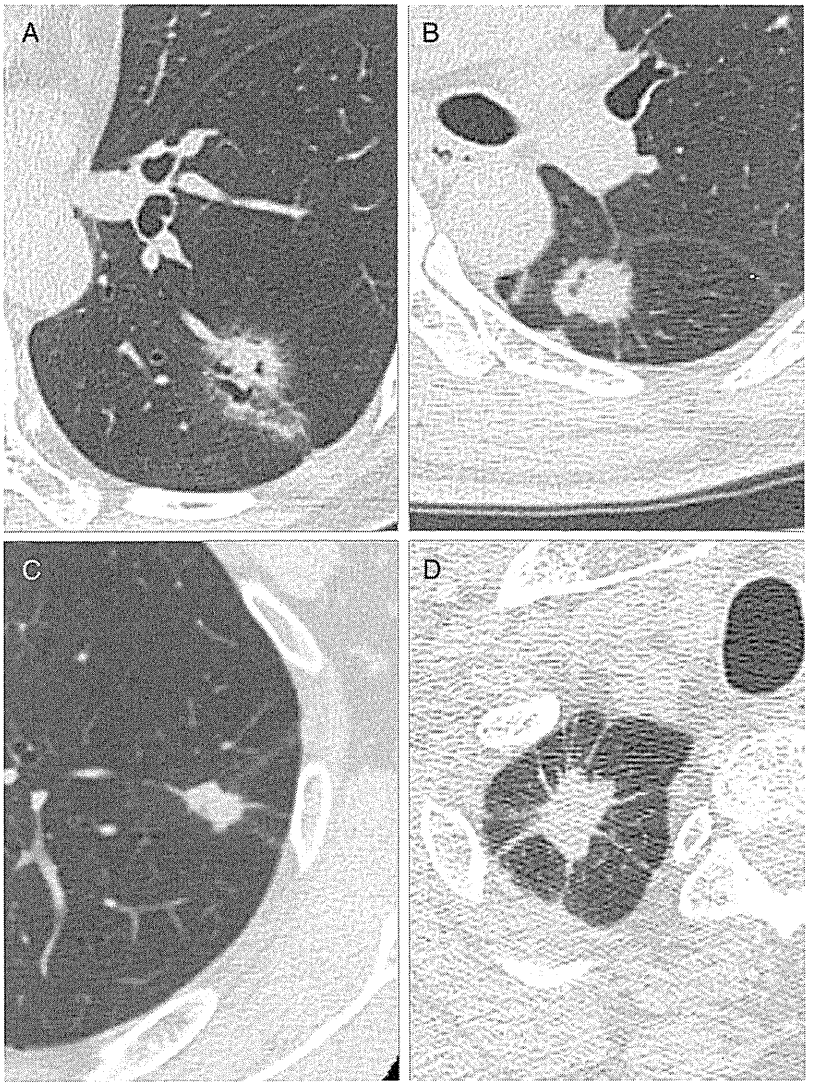

Figure 3: (**A**) A 58-year old female had a 2.8-cm part-solid nodule in the left lower lobe of the lung with spicula. The nodule was classified into Category 5. Lobectomy without an intraoperative diagnosis was performed. The final pathological diagnosis showed the nodule to be invasive adenocarcinoma. (**B**) A 65-year old male had a 2.0-cm solid nodule in the left lower lobe of the lung with a contrast enhancement of 50 hounsfield units (HU), SUVmax of 5.0 and spicula. The nodule was classified into Category 5. Lobectomy without an intraoperative diagnosis was performed. The final pathological diagnosis showed the nodule to be invasive adenocarcinoma. (**C**) A 77-year old male had a 2.2-cm solid nodule in the left upper lobe of the lung with a contrast enhancement of 8 HU and a SUVmax of 2.2. The nodule was classified into Category 3. Wedge resection with an intraoperative frozen section diagnosis showed the nodule to be a granuloma. (**D**) A 77-year old male had a 1.9-cm solid nodule in the right upper lobe of the lung with a contrast enhancement of 17 HU, SUVmax of 5.9 and spicula. The nodule was classified into Category 5. Wedge resection with an intraoperative frozen section diagnosis showed the nodule to be a granuloma.

monoxide (DLCO), surgical approach and lymph node dissection were not.

Table 3 reports the results of the multivariate logistic regression analysis for postoperative morbidity and a prolonged hospital stay in the 232 patients. The length of the operation and ppoDLCO were significant factors predicting both postoperative morbidity ($P = 0.0040$ and 0.0415, respectively) and a prolonged hospital stay ($P = 0.0312$ and 0.0014, respectively).

In the whole cohort, including 202 patients with a preoperative definitive diagnosis, we also performed the multivariate logistic regression analysis by treating the preoperative diagnosis and intraoperative diagnosis as variables instead of the length of the operation. Either the preoperative diagnosis or intraoperative diagnosis was not a significant factor predicting either the postoperative morbidity or a prolonged hospital stay.

DISCUSSION

Transbronchial biopsy with a flexible bronchoscope and CT-guided needle biopsy of lung tumours are often used to establish a preoperative malignant diagnosis. These examinations help avoid unnecessary surgery and the labour for intraoperative diagnostic procedures. Furthermore, definitive pathological diagnostic confirmation is necessary for neoadjuvant therapy. However, these are associated with potential risks of physical complications, such as bleeding, pneumothorax and false-negative, false-positive and non-diagnostic results [6, 17–19]. Additionally, CT-guided needle biopsy is associated with the risk of implanting cancer cells in the needle track and pleura, and of causing an air embolism [17, 20, 21]. Therefore, a surgical approach without a preoperative definitive diagnosis is frequently preferred when the probability of

Table 2: The characteristics of patients with and without an intraoperative diagnosis

Intraoperative diagnosis	Total	Yes			No			*P*-value
		Wedge resection	Segmentectomy	Lobectomy	Wedge resection	Segmentectomy	Lobectomy	
Number	232	12	14	56	17	31	102	
Age [(mean ± SD), years]	68.7 ± 8.3	71.2 ± 5.2	65.4 ± 10.9	66.5 ± 9.0	71.3 ± 7.7	71.9 ± 7.1	68.7 ± 7.9	0.0263
Sex								
Female	85	2	7	13	5	9	49	0.0115
Male	147	10	7	43	12	22	53	
Smoking status								
Never	82	2	6	17	6	9	42	0.4072
Current or former	150	10	8	39	11	22	60	
Nodule size [(mean ± SD), cm]	2.2 ± 0.9	1.4 ± 0.6	1.7 ± 0.6	2.1 ± 0.9	1.4 ± 0.4	2.2 ± 1.0	2.6 ± 0.9	<0.0001
Probability category								
Category 3	29	5	3	13	6	1	1	<0.0001
Category 4	46	5	2	14	6	4	15	
Category 5	157	2	9	29	5	26	86	
ppoFEV1, % of predicted (mean ± SD)	87.9 ± 19.2	90.8 ± 20.2	101.4 ± 15.5	84.7 ± 14.2	102.6 ± 19.5	93.1 ± 25.7	83.5 ± 17.4	<0.0001
ppoDLCO, % of predicted (mean ± SD)	92.4 ± 25.4	100.6 ± 28.6	99.0 ± 20.7	88.6 ± 25.3	99.9 ± 35.3	103.5 ± 25.4	87.9 ± 22.5	0.0181
Surgical approach								
Thoracotomy	198	8	14	53	4	29	90	<0.0001
VATS	34	4	0	3	13	2	12	
Lymph node dissection								
Sampling	60	12	2	5	17	12	12	<0.0001
Systematic	172	0	12	51	0	19	90	
Pathological diagnosis								
Lung cancer	214	6	14	51	11	30	102	<0.0001
Other malignant tumour	11	2	0	5	3	1	0	
Benign tumour	7	4	0	0	3	0	0	
Length of operation [(mean ± SD), min]	177.8 ± 68.0	105.3 ± 41.2	205.7 ± 61.3	212.3 ± 72.3	85.8 ± 30.3	177.1 ± 53.3	179.2 ± 57.1	<0.0001
Postoperative morbidity								
No	178	12	12	45	15	25	69	0.0184
Yes	54	0	2	11	2	6	33	
Prolonged hospital stay								
No	214	12	13	51	16	30	92	0.5762
Yes	18	0	1	5	1	1	10	

SD: standard deviation; ppo: predicted postoperative; FEV1: forced expiratory volume in the first second; DLCO: diffusing capacity of the lung for carbon monoxide; VATS: video-assisted thoracic surgery.

Table 3: The results of the multivariate logistic regression analysis for postoperative morbidity and a prolonged hospital stay

	Postoperative morbidity				Prolonged hospital stay			
	OR	95% CI		*P*-value	OR	95% CI		*P*-value
Age (10-year increase)	1.546	0.996	2.483	0.0520	1.986	0.934	4.695	0.0764
Sex								
Female	1.000				1.000			
Male	1.054	0.420	2.691	0.9118	3.247	0.718	17.685	0.1296
Smoking status								
Never	1.000				1.000			
Current or former	1.277	0.502	3.324	0.6090	0.763	0.174	3.594	0.7242
Nodule size (1-cm increase)	1.163	0.813	1.655	0.4041	0.999	0.537	1.752	0.9981
ppoFEV1, % of predicted (10% increase)	0.984	0.808	1.198	0.8723	1.060	0.771	1.459	0.7172
ppoDLCO, % of predicted (10% increase)	0.856	0.734	0.994	0.0415	0.676	0.515	0.863	0.0014
Surgical procedure								
Wedge resection	1.000				1.000			
Segmentectomy	0.986	0.145	8.913	0.9890	0.624	0.013	28.749	0.7957
Lobectomy	1.399	0.224	12.070	0.7290	0.797	0.021	32.250	0.8950
Surgical approach								
Thoracotomy	1.000				1.000			
VATS	0.558	0.120	1.909	0.3727	2.332	0.283	13.023	0.3908
Lymph node dissection								
Sampling	1.000				1.000			
Systematic	1.287	0.475	3.824	0.6278	3.724	0.578	74.640	0.1863
Length of operation (30-min increase)	1.264	1.076	1.498	0.0040	1.276	1.022	1.615	0.0312

OR: odds ratio; CI: confidence interval; SD: standard deviation; ppo: predicted postoperative; FEV1: forced expiratory volume in the first second; DLCO: diffusing capacity of the lung for carbon monoxide; VATS: video-assisted thoracic surgery.

malignancy is high and the surgical risk is low, which can reduce the interval between presentation and surgery [6, 22]. In the current study, nodules classified into Category 4 and 5 were considered good candidates for surgery even without a preoperative definitive diagnosis, resulting in a high rate (99%) of malignancy. By contrast, nodules classified into Category 3 were not always recommended for surgery, but often recommended for follow-up or biopsy. However, this subgroup, we performed surgery for 29 nodules as an option when a patient preferred surgical diagnosis to follow-up and biopsy, resulting in wedge resection in five (17%) benign tumours.

Only a few studies have so far assessed the validity of performing therapeutic surgery without a preoperative or intraoperative definitive diagnosis. In 1984, Keagy *et al.* [23] reported that lobectomy for 102 patients whose tumours were suspected to be lung cancer, without a preoperative or intraoperative diagnosis, was recommended regarding the safety and the completeness of resection, resulting in a 68% rate of discovery of malignancy. Moreover, non-invasive radiological modalities have recently been developed to distinguish lung cancer from benign tumours. In the current study, we evaluated the risks and benefits of therapeutic surgery without a definitive diagnosis based on the estimation of the probability of lung cancer using the current radiographic modalities.

The benefits of this management are the many direct effects of saving time and costs. First, our results suggest that it decreases the length of the operation, which was a significant factor associated with the postoperative morbidity and a prolonged hospital stay. However, we should comment that either the preoperative diagnosis or intraoperative diagnosis was not a significant factor predicting either the postoperative morbidity or a prolonged hospital stay. This is one of the weak points of the current study. Second, it saves on the cost of devices such as the staplers or needles used for the diagnostic procedures. Third, it would save the risk of a second operation and the pathologists' labour and responsibility for instant decision-making for an intraoperative consultation on a frozen section or a needle biopsy. An intraoperative diagnosis based on frozen sections and needle biopsies is known to have limitations due to the potential risks of physical complications, false-negative results and the implantation of cancer cells [6, 20, 23, 24]. The sensitivity and specificity of the frozen section diagnosis for malignancy reported by Marchevsky *et al.* were 87–94 and 100%, respectively, in patients with nodules that measured ≤1.5 cm [24]. In the current study, the diagnostic accuracy of an intraoperative diagnosis for malignancy (95%) was lower than that of Category 5 based on the imaging findings (99%), although the cases could not be directly compared.

The risk of such management is the possibility of performing oversurgery for benign tumours without a pathological confirmation. The high specificity of the intraoperative diagnosis reported by Marchevsky *et al.* implies an advantage of avoiding oversurgery. However, none of our consecutive 233 patients underwent lobectomy for benign tumours. This suggests that avoiding oversurgery can be achieved, especially with careful attention given to granulomatous disease.

With regard to the limitations of this retrospective study, an exact practical algorithmic approach was not used for the probability estimate of lung cancer. Some studies have indicated that clinical judgement and algorithmic models based on patient characteristics and CT scans appear to have similar accuracy for diagnosing malignant lung nodules [25]. In the current study, the probability classification was highly dependent on the judgement by one radiologist based on the findings on thin-section CT and PET–CT scans.

The other limitation of this study comes from the small number of benign tumours. However, this very result might support the usefulness of the current radiographic modalities in patient selection for surgery.

In conclusion, this study provides important information regarding the necessity of a definitive diagnosis before therapeutic surgery in patients with suspected lung cancer. Provided that there is a careful clinical decision and informed consent, patients with a high probability of lung cancer based on the diagnostic imaging findings are good candidates for therapeutic surgery, even without a preoperative or intraoperative definitive diagnosis.

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Prognostic value of intraoperative pleural lavage cytology for non–small cell lung cancer: The influence of positive pleural lavage cytology results on T classification

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Objective: Although positive pleural lavage cytology (PLC) has been demonstrated to be closely associated with a poor prognosis for patients with lung cancer, it has not been incorporated into the TNM staging system of the Union for International Cancer Control. The aim of our study was to retrospectively examine the clinical significance of PLC status and illustrate the recommendations of the International Pleural Lavage Cytology Collaborators (IPLCC) in a large national database.

Methods: The Japanese Joint Committee of Lung Cancer Registry database included 11,073 patients with non–small cell lung cancer who underwent resections in 2004. We extracted the clinicopathologic data for 4171 patients (37.3%) who underwent PLC. These patients were staged according to the seventh edition of the Union for International Cancer Control TNM classification and by recommendations of the IPLCC, in which T was singly upgraded up to a maximum of T4 for those who were PLC-positive. Prognoses based on these 2 systems were compared.

Results: A total of 217 patients (5.2%) were PLC-positive, which was significantly associated with a higher incidence of adenocarcinoma and advanced disease. The 5-year survival for patients with positive and negative PLC results were 44.5% and 72.8%, respectively, and this difference in survival was statistically significant ($P < .001$). Multivariate analysis showed that positive PLC status was an independent factor for a poor prognosis (hazard ratio, 1.57; $P < .001$). Significant differences in survival were also found between patients with positive and negative PLC results in the same T categories and stages, including T2a, T3, stage IB, and stage IIIA. The IPLCC recommendations adjusted the prognostic differences in all T categories and stages. The significant difference in survival disappeared between the 2 groups in all T categories and stages.

Conclusions: Our results indicate that a T category upgrade is prognostically adequate for patients who are PLC-positive. (J Thorac Cardiovasc Surg 2014;148:2659-64)

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For surgical cases of primary lung cancer, pleural lavage cytology (PLC) is a simple, easily done technique that provides a cytodiagnosis at the time of thoracotomy to evaluate subclinical pleural dissemination of cancer cells without pleural dissemination or pleural effusion. After a PLC result was first reported by Eagan and colleagues[1] in 1984, numerous studies have shown that PLC status is a prognostic factor for primary lung cancer.[2-22] In general, the frequency of positive results is <10% of patients who underwent PLC in the larger published series. In previous multiinstitution studies, a positive PLC result was suggested to be an independent prognostic factor and a predictor of tumor recurrence.[22-26]

However, PLC findings were not incorporated in the TNM Classification of Malignant Tumours.[27,28] In 2010, the

Abbreviations and Acronyms

IPLCC = International Pleural Lavage Cytology Collaborators
NSCLC = non–small cell lung cancer
PLC = pleural lavage cytology
UICC = Union for International Cancer Control

International Pleural Lavage Cytology Collaborators (IPLCC) reported the results of a meta-analysis and recommended that a single increase in the T category up to a maximum of T4 be assigned to patients with positive PLC results.[24]

The aim of our study was to retrospectively examine the clinical significance of PLC status and to illustrate the recommendations of the IPLCC. We used a large national database that were compiled by the Japanese Joint Committee of Lung Cancer Registry.[29,30]

PATIENTS AND METHODS

In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study on the prognosis and clinicopathologic profiles of resected lung neoplasms in Japan.[29,30] Only primary lung neoplasms that had been resected in 2004 at certified teaching hospitals in Japan were considered for the registry, which provided a follow-up period of at least 5 years. The committee received the registries of 11,663 patients from 253 teaching hospitals.

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 published June 17, 2002, which were revised August 16, 2007. In addition, it was approved by the institutional review board of Osaka University Medical Hospital, where the registry office is located, after discussions were published August 13, 2009 (approval No. 09124).

The patients in this study were 4171 patients who underwent PLC from among 11,073 patients with non–small cell lung cancer (NSCLC) (37.3%). Cases involving malignant pleural effusion were excluded. There were 2524 men and 1647 women. Adenocarcinoma was detected in 2977 patients, squamous cell carcinoma in 881 patients, large cell carcinoma in 149 patients, adenosquamous carcinoma in 81 patients, and other histologic types in 83 patients. The seventh edition of the Union for International Cancer Control (UICC) TNM classification system was used for the evaluations of TNM staging.[25] There were 1694 patients in stage IA, 1009 patients in stage IB, 378 patients in stage IIA, 262 patients in stage IIB, 703 patients in stage IIIA, 38 patients in stage IIIB, and 87 patients in stage IV. In our study, the PLC technique used had not been standardized. Induction therapy was performed in 199 patients (chemotherapy in 118 patients, radiation therapy in 6 patients, and chemoradiotherapy in 75 patients). Adjuvant chemotherapy was administered to 977 patients. These menus were not uniform.

To correct the prognoses according to the pathologic stages of patients with positive PLC results to patients with negative PLC results, pathologic stages were reevaluated based on the recommendations of the IPLCC: a single increase in the p-T category up to a maximum of T4 was assigned to patients with a positive PLC result (upstage).[24] Single increases in the T category upstaged T1a to T1b, T1b to T2a, T2a to T2b, T2b to T3, and T3 to T4. Pathologic stages were rearranged according to the upstaged T categories.

Categorical data are presented as frequency and continuous data are presented as means with standard deviations. Comparisons of categorical data between the 2 groups were made using χ^2 tests or Fisher exact tests where appropriate and continuous data were compared using 2-tailed t test. The survival time was measured from the date of surgery to the death date or the last follow-up date. The survival curves were estimated by using the Kaplan-Meier method. Differences in survival were assessed by the log-rank test. Multivariate analyses of prognostic factors were carried out using Cox proportional hazard regression models. A P value <.05 was considered to be significant.

RESULTS

Among 4171 patients who underwent PLC, 217 patients (5.2%) had positive PLC results (Table 1). Patients with positive PLC results had larger tumors ($P < .0001$) and more frequently adenocarcinoma in the histology ($P < .0001$), advanced stage ($P < .0001$), and pleural invasion ($P < .0001$) in comparison with those who were PLC-negative.

Sixty-five percent of patients with positive PLC and 29.2% of PLC-negative patients developed recurrence within 5 years after surgery ($P < .0001$). The 5-year survival was 44.5% for patients with positive PLC results and was 72.8% for patients with negative PLC results ($P < .0001$) (Figure 1). By multivariate analysis using a Cox proportional hazard regression model, PLC status (hazard ratio, 1.57; 95% confidence interval, 1.276-1.919; $P < .0001$) and other clinical factors (ie, gender, age, T category, N category, M category, and tumor size) were independent prognostic factors (Table 2).

Comparisons of the survival between patients with positive and negative PLC results according to T categories revealed significant differences in T2a ($P < .0001$) and T3 ($P = .0184$) (Figure 2 and Table 3). In addition, comparisons of the survival between patients with positive and negative PLC results according to pathologic stages revealed significant differences in stage IB ($P = .0062$) and stage IIIA ($P = .0115$) (Table 3). Based on the recommendations of the IPLCC, if a single increase in the T category up to a maximum of T4 was assigned to a patient with a positive PLC result, the significant difference in survival disappeared between the 2 groups in all T categories and stages. (Figure 3 and Table 4).

DISCUSSION

Body cavity fluid cytology is a simple, easily done technique that provides an intraoperative cytodiagnostic evaluation of latent dissemination of cancer cells.[31] In surgical cases of abdominal malignant tumors, PLC status is an independent prognostic factor, as reflected in the UICC TNM classification for gastric, uterine, ovarian, and fallopian tube cancers.[28] PLC status is directly involved in the treatment strategy. However, PLC findings were not incorporated in the seventh edition of the UICC TNM staging system.[28,32] It is not known to what extent the noninclusion of PLC results affects treatment strategies.

In this study, 5.2% of patients who underwent PLC had positive results. When these patients were examined by T,

TABLE 1. Clinicopathologic characteristics according to pleural lavage cytology (PLC) results

Characteristic	Positive PLC	Negative PLC	*P* value
Age (y)	66.2 ± 9.9	66.3 ± 9.8	.9040
Gender			.0640
Male	118	2406	
Female	99	1548	
Histologic type			<.0001
Adenocarcinoma	193	2784	
Squamous cell carcinoma	19	862	
Others	5	308	
Surgical procedure			.0460
Pneumonectomy	9	121	
Lobectomy	177	3239	
Segmentectomy	14	321	
Wedge resection	10	234	
Others	7	38	
T category			<.0001
T1a	14	1147	
T1b	12	771	
T2a	138	1390	
T2b	9	186	
T3	35	394	
T4	9	66	
N category			<.0001
N0	109	3040	
N1	26	318	
N2	81	584	
N3	1	12	
M category			<.0001
M0	187	3886	
M1a	27	30	
M1b	3	38	
Pathologic stage			<.0001
IA	15	1679	
IB	60	949	
IIA	23	355	
IIB	12	250	
IIIA	74	629	
IIIB	4	34	
IV	29	58	
Tumor size (cm)	3.40 ± 1.63	2.99 ± 1.80	
Pleural factor			<.0001
pl 0	47	2759	
pl 1	56	669	
pl 2	85	229	
pl 3	25	279	
Not evaluated	4	18	
Total	217	3954	

PLC, Pleural lavage cytology.

N, and M categories and by pathologic stages, significantly higher percentages of advanced cases were seen among patients with positive PLC results compared with patients with negative PLC results. Patients with positive PLC results also had significantly larger tumors than those who were PLC-negative. A significantly higher percentage of

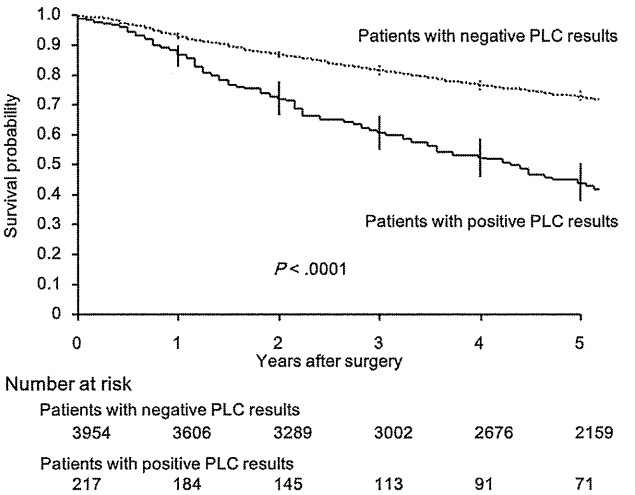

FIGURE 1. Postoperative survival curves based on pleural lavage cytology (*PLC*) status. There was a significant difference between patients with positive and negative PLC results ($P < .0001$). The *solid line* indicates patients with positive PLC results and the *dashed line* indicates patients with negative PLC results. The *vertical bars* indicate 95% confidence intervals.

pleural invasion was evident among patients with positive PLC results compared with those who were PLC-negative. These characteristics are consistent with those described in previous reports.[1,9,10,12,14,19] In our study, the 5-year survival was 44.5% for patients with positive PLC results and 72.8% for patients with negative PLC results, which indicated a significantly worse prognosis for patients with positive PLC results. A multivariate analysis revealed that PLC finding is an independent prognostic

TABLE 2. Multivariate analysis for prognostic factors

Prognostic factor	Hazard ratio	95% Confidence interval	*P* value
Positive PLC	1.57	1.276-1.919	<.0001
Male gender	1.66	1.460-1.894	<.0001
Age, per year	1.03	1.023-1.036	<.0001
T category			
T1a	1.00	—	—
T1b	1.59	1.266-1.990	<.0001
T2a	2.01	1.645-2.461	<.0001
T2b	2.79	2.048-3.794	<.0001
T3	2.94	2.271-3.807	<.0001
T4	3.87	2.692-5.564	<.0001
N category			
N0	1.00	—	—
N1	1.76	1.459-2.111	<.0001
N2	3.13	2.735-3.580	<.0001
N3	9.27	5.083-16.913	<.0001
M category			
M0	1.00	—	—
M1a	1.89	1.349-2.643	<.0001
M1b	4.02	2.601-6.206	<.0001
Tumor size (cm)	1.05	1.014-1.085	.006

PLC, Pleural lavage cytology.

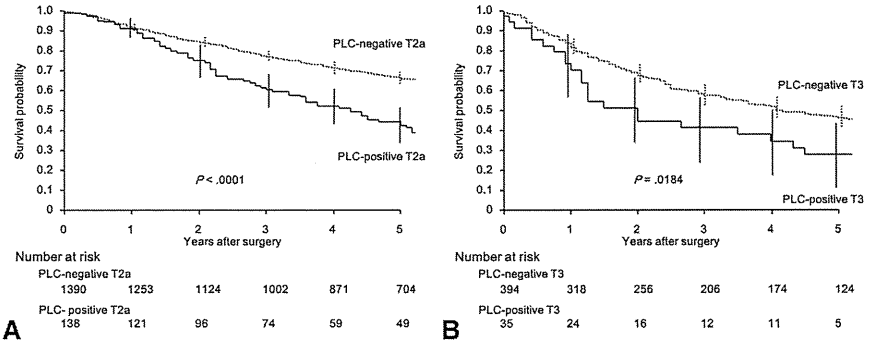

FIGURE 2. Comparisons of survival curves between patients with positive and negative pleural lavage cytology (*PLC*) results based on T categories. A, There was a significant difference between PLC-positive T2a and PLC-negative T2a ($P < .0001$). B, There was a significant difference between PLC-positive T3 and PLC-negative T3 ($P = .2261$). *Solid lines* indicate patients with positive PLC results and *dashed lines* indicate patients with negative PLC results. The *vertical bars* indicate 95% confidence intervals.

factor with a hazard ratio of 1.57. PLC status has been suggested to be an independent prognostic factor in previous reports.[6,12,14,16,19,21] Some reports only recognized certain stages as an independent factor and other reports stated that PLC status was not an independent prognostic factor.[17,18] Recent studies that used meta-analyses have shown that PLC status is an independent prognostic factor.[23,24,26] However the time periods considered in these studies covered a wide range. In our study, patients were limited to those who underwent surgery during 2004; thus, patients were evaluated and treated according to a relatively standardized procedure.

The prognoses for patients with positive and negative PLC results were compared by T category and pathologic stage based on the seventh edition of the UICC TNM classification. Significant differences in survival were found between the patients with positive and negative PLC results within the same T category and stage, including T2a, T3, stage IB, and stage IIIA. One reason for these findings may be differences in the number of patients in each group. For example, the T2a and T3 stages included more patients than the other T subclassifications. Similarly, the stage IB and stage IIIA categories included more patients than the other subgroups. Based on the sixth edition of the UICC TNM classification, the IPLCC recommended that a single increase in the T category up to a maximum of T4 be assigned to those with positive PLC results.[24] We performed a single increase in the T category based on the seventh edition of the TNM classification. The significant differences in the survival between patients with positive and negative PLC results disappeared for all T categories and stages.

TABLE 3. Comparisons of survival rates between patients with positive and negative pleural lavage cytology (PLC), according to T categories and pathologic stages

	Positive PLC		Negative PLC		
Category or stage	n	5-y survival (%)	n	5-y survival (%)	*P* value
T category					
T1a	14	76.2	1147	88.3	.2977
T1b	12	71.3	771	79.2	.1951
T2a	138	45.1	1390	67.7	<.0001
T2b	9	25.0	186	53.7	.1100
T3	35	27.7	394	46.4	.0184
T4	9	19.4	66	36.2	.9587
Pathologic stage					
IA	15	100	1679	88.8	—
IB	60	61.5	949	77.1	.0062
IIA	23	48.3	355	62.9	.0833
IIB	12	37.0	250	51.8	.5496
IIIA	74	26.4	629	42.5	.0115
IIIB	4	37.5	34	20.2	.2912
IV	29	27.8	58	30.3	.4962
Total	217	44.5	3954	72.8	<.0001

PLC, Pleural lavage cytology.

The significance of incorporating PLC findings into the TNM classification system is reflected in the treatments for upstaged patients, such as the addition of adjuvant therapy or a change to a more effective adjuvant therapy. There have been some proposals for incorporating PLC findings in the TNM classification system in which patients with positive PLC results were classified into T3 disease,[25] T4 disease,[9,21] or stage IIIB disease.[14] However there was no consensus among these proposals because most of these series were too small for detailed analysis. Moreover, because PLC status is related to multiple prognostic factors, it may be inappropriate for patients with positive PLC results to be classified into a single T category or single stage. The IPLCC recommendation should be the most reliable proposal because it is based on an exploratory statistical model using data from a multiinstitution study.

This study is associated with several limitations that should be considered when interpreting the results. First, the PLC technique has not been standardized. The IPLCC recommends that 100 mL saline be irrigated over the lung