Noncancerous lesions

A total of 38 noncancerous patients underwent pulmonary resection because of a preoperative diagnosis of lung cancer or suspected lung cancer. Seven of them were preoperatively misdiagnosed pathologically as having lung cancer. The definitive diagnoses for these lesions are shown in Table 3. There were two patients each with inflammatory pulmonary tumors and atypical adenomatous hyperplasia. Granuloma, tuberculoma, and sarcoma were seen in one patient each.

Altogether, 31 noncancer patients underwent pulmonary resection without a preoperative pathological diagnosis (Table 4). Inflammatory pulmonary tumors (n = 10) were the most common pathology radiologically misdiagnosed as lung cancer.

Table 3 Noncancerous lesions with preoperative pathological diagnosis of lung cancer (n = 7)

Lesion	No.
Inflammatory pulmonary tumor	2
Atypical adenomatous hyperplasia	2
Granuloma	1
Tuberculoma	1
Sarcoma	1

Table 4 Noncancerous lesion without a preoperative pathological diagnosis (n = 31)

Lesion	No.
Inflammatory pulmonary tumor	10
Granuloma	4
Cryptococcoma	4
Amyloidoma	3
Hamartoma	2
Tuberculoma	2
Lymphoma	1
Others	5

Diagnostic yield of CT imaging

Among the 1755 patients who underwent surgery, 1717 were definitively confirmed as having lung cancer; thus, the diagnostic yield of preoperative CT imaging was 97.8% (1717/1755). Furthermore, among the 466 s/o lung cancer patients, the results of 435 were found at surgery to be compatible with the predicted findings of lung cancer, and the diagnostic yield for surgical intervention was thus 93.3% (435/466) (Table 5).

Discussion

Recent advances in CT imaging have increased the detection rate for peripherally located small pulmonary nodules. As shown in Table 2, the main factor contributing to the increase in the preoperative nondiagnostic rate was small adenocarcinomas recognized on CT.

Several studies, mainly focusing on the evaluation of morphological characteristics and on the differentiation between malignant and benign pulmonary lesions reported that the sensitivity, specificity, and accuracy of high-resolution and spiral CT techniques were 89%–94%, 57%–65%, and 79%–84%, respectively (Table 6).[5,15,16] Recent studies focusing on the hemodynamic characteristics of dynamic helical CT set the cutoff threshold at 15–30 HU and reported sensitivities of 81%–99%, specificities of 54%–93%, and accuracies of 77%–92% (Table 6).[9–12,16] The sensitivity was almost

Table 5 Correspondence of the definitive diagnosis and preoperative pathological diagnosis

Preoperative pathological diagnosis	Definitive diagnosis		Total
	Lung cancer	No cancer	
Yes	1282	7	1289
No	435	31	466
Total	1717	38	1755

Table 6 Diagnostic yields of CT based on morphological features and hemodynamic characteristics

Study	Year	Evaluation	No. of nodules	Sensitivity (%)	Specificity (%)	Accuracy (%)
Seemann[15]	1999	Morpho	104	91	57	84
Seemann[5]	2000	Morpho	104	89	61	83
Swensen[9]	2000	Hemody	356	98	58	77
Yi[10]	2004	Hemody	131	99	54	78
Jeong[11]	2005	Hemody	107	94	90	92
Yi[12]	2006	Hemody	119	81	93	85
Lee[16]	2007	Morpho and hemody	486	94* (89) [92]	65* (79) [79]	79* (84) [86]

Morpho, morphological features; Hemody, hemodynamic characteristics
*Rate based on morphological features; ( ), rate based on hemodynamic characteristics; [ ], rate based on both morphological features and hemodynamic characteristics

equivalent to the evaluations of morphological features and hemodynamic characteristics. The specificity tended to be lower than that with the evaluation of hemodynamic characteristics. Furthermore, when both hemodynamic characteristics and morphological features were evaluated, the sensitivity, specificity, and accuracy were better than the evaluation by hemodynamic characteristics alone.[12]

Recently, there has been an increase in the number of studies investigating the differences between CT and other imaging modalities for evaluating solitary pulmonary nodules. Reports demonstrating the benefit of non-CT modalities are occasionally documented. However, a meta-analysis comparing representative imaging modalities—dynamic CT, dynamic magnetic resonance imaging (MRI), ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), ^{99m}Tc-depreotide single photon emission computed tomography (SPECT)—showed that there are no significant differences among these tests.[17] As described above, we believe that it is possible to evaluate solitary pulmonary nodules in detail using CT alone. Because we focused only on suspected malignant lesions, a sufficient evaluation could not be conducted for sensitivity, specificity, accuracy, or positive and negative predictive values, but 1717 of 1755 p/p lung cancer and s/o lung cancer patients (97.8%) were definitively diagnosed with lung cancer. Moreover, among the 466 s/o lung cancer patients who underwent surgical intervention based on CT findings and the clinical judgment of various experts, the results of 435 were compatible with the predicted findings of lung cancer (93.3%, 435/466). This diagnostic yield for pulmonary nodules without a preoperative diagnosis is acceptable.

If indeterminate pulmonary lesions detected by chest radiography and/or CT are not difficult to confirm pathologically, how do we pursue a diagnosis with no surgical procedure? Diagnostic procedures using flexible bronchoscopy (FB) (e.g., bronchial brushing, bronchial washing, transbronchial biopsy) are mainly pathological diagnostic modalities. A review in the American College of Chest Physicians (ACCP) clinical practice guidelines indicated that the sensitivity of FB was 78% for the diagnosis of peripheral lesions, although it was 88% for diagnosing central disease. Furthermore, the sensitivity was 34% for peripheral lesions <2 cm in diameter.[18]

Compensating for the shortcomings of FB, CT-guided transthoracic needle biopsy (CTNB) is almost established as an important alternative procedure to diagnose peripherally located pulmonary lesions that are not accessible by FB or not visible on radiographs. However, there are several fatal complications associated with CTNB including coronary and cerebral infarction due to air embolism.[19,20] Pleural dissemination after CTNB has also been reported, despite the fact that lesions are recognized at an early stage of surgery.[21,22] Ost et al. and the ACCP evidence-based clinical practice guidelines recommend surgical resection for suspected malignant pulmonary nodules.[14,23] Considering the harm caused by CTNB, an invasive diagnostic procedure, its use at our institution has gradually decreased. It is performed in only a limited number of patients who do not desire surgery but who must undergo other treatments, such as chemotherapy and irradiation, based on histopathological features.

Surgical resection is the standard diagnostic procedure. The advantage of surgical intervention under general anesthesia is that it can be changed to oncological resection and include a lymphadenectomy based on the intraoperative pathological diagnosis during the same procedure. Intraoperative histopathological consultations have high diagnostic accuracy.[24] We also perform the same surgical intervention when we encounter suspected malignant and surgical candidates with a pulmonary lesion. In our study, the intraoperative diagnostic yield (needle biopsy using a TMU needle and partial resection) and the definitive diagnostic rate of lung cancer in patients without a preoperative pathological diagnosis were 61.6% (268/435) and 93.3% (435/466), respectively. We believe that the diagnostic yield by surgical resection for suspected lung cancer is high enough to be acceptable for suspected lung cancer patients. False-positive rates for patients who undergo pulmonary resection for lung cancer or suspected lung cancer are admissible.

Although the importance of preoperative pathological diagnosis remains highly valued, clinical judgment is also important as recommended by the ACCP clinical practice guidelines.[14] Patients with suspected malignant lesions benefit if doctors chose to perform a surgical intervention based on a well-considered radiographic evaluation and clinical judgment rather than taking an unnecessarily long time for a preoperative pathological diagnosis.

Conclusion

Our study results showed that the diagnostic yields of CT imaging for lung cancer and suspected lung cancer, based on an evaluation from various experts, were sufficiently high. Furthermore, surgical diagnostic procedures are acceptable if the clinical probability of malignancy is high, including the above-listed radiological features, and the malignancy is pathologically undiagnosed.

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Prognostic Heterogeneity in Multilevel N2 Non-Small Cell Lung Cancer Patients: Importance of Lymphadenopathy and Occult Intrapulmonary Metastases

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Background. To evaluate prognostic heterogeneity that may exist in multilevel N2 non-small lung cancer, we attempted to identify clinicopathologic prognostic factors for multilevel N2 patients who underwent standard surgeries.

Methods. We retrospectively evaluated records from 1988 to December 2007 for 106 non-small lung cancer patients diagnosed with multilevel N2 disease by postoperative pathologic examination (49 women, 57 men; median age = 61 years). Patients with clinical T4 (cT4) and bulky N2 (shortest mediastinal lymph node diameter >2 cm) disease were excluded from the study. Follow-up periods ranged from 2 to 240 months (median for living patients = 36 months). Records were examined for age, sex, preoperative nodal status (cN2 versus cN0 or cN1), primary tumor sites, surgical procedure, metastatic stations (distribution and numbers), tumor sizes, histologic features, and adjuvant therapies.

Results. By univariate analysis, cN (cN2), intrapulmonary metastases within the same lobe of the primary tumor (PM), and male sex were significant adverse prognostic factors; smoking only tended toward significance ($p = 0.1$). Other clinicopathologic variables were not significant prognostic factors. By multivariate analysis, cN (cN2) and PM were significant prognostic factors. Patients who had neither cN2 nor PM had significantly higher survival rates than those who had either cN2 or PM (5-year survival rates of 36.5% and 11.2%, respectively).

Conclusions. Multilevel N2 patients can be grouped according to the prognostic factors cN2 and PM. These findings have potential for evaluating the best therapeutic modalities or agents for multilevel N2 patients.

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For non-small cell lung cancer (NSCLC) patients with p-N2, it has been reported that clinical factors, such as c-N (c-N2), skip N2 metastasis (non-skip N2), and the N2 level (multiple station metastases or multilevel N2), were associated with worse prognoses [1–6]. In particular, multilevel N2 is one of the established adverse prognostic factors for N2 patients [4–6]. It has been shown that multilevel N2 patients showed much poorer prognoses (9% to 23% for 5-year survivals) than those with single-level N2 (25% to 60% for 5-year survivals) [1–6].

Once patients are diagnosed with multilevel N2, they are considered for multimodal treatments as parts of some clinical studies. When we evaluate the therapeutic options for multilevel N2 patients, it is very important to consider the multiple prognostic factors that may exist in these groups, as they are typically very heterogeneous. However, there have been few reports that have considered the prognostic factors focusing on multilevel N2 patients, mainly because of their poor outcomes.

Recently, a new diagnostic modality, real-time endobronchial ultrasonography-guided transbronchial needle aspiration cytology, has enabled the diagnosis of mediastinal lymph node metastasis in a less invasive manner than with previous methods [7]. This new modality has improved the accuracy for the diagnosis of mediastinal lymph node metastasis, even for patients without mediastinal lymph node adenopathy. Therefore, the proportion of NSCLC patients with multilevel N2, which would not have been detected before, has changed. The proportion of multilevel N2 patients without mediastinal lymphadenopathy must be especially increased in the population. It is unclear until now whether multilevel N2 patients without mediastinal lymphadenopathy show the same prognosis as patients with mediastinal lymphadenopathy.

To clarify prognostic heterogeneity that may exist in multilevel N2 NSCLC, we attempted to identify clinicopathologic prognostic factors for patients with pathologically proven multilevel N2 who had undergone standard

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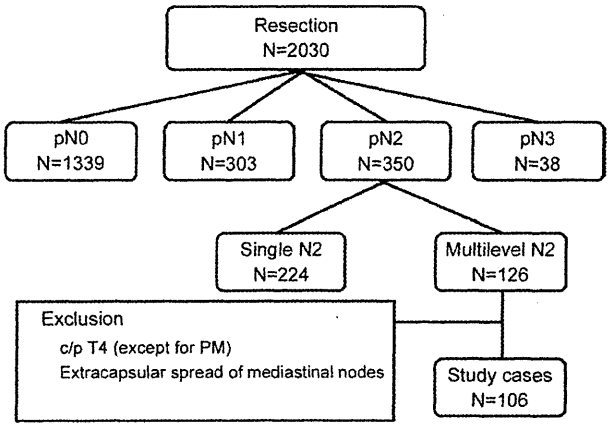

Fig 1. Diagram indicating study group subdivisions. Between 1988 and December 2007, 2,030 patients underwent surgical resections for primary lung cancer at the Cancer Institute Hospital. (PM = intrapulmonary metastases.)

surgeries. These results may provide opportunities to make more relevant evaluations of therapeutic strategies or new agents for multilevel N2 patients.

Patients and Methods

This was a retrospective study. As individual patients were not identified, our institutional review board waived the requirement to obtain patient consent and approval for this study.

Between 1988 and December 2007, 2,030 patients underwent surgical resections for primary lung cancer in the Cancer Institute Hospital. Among these patients, 350 were diagnosed with N2 disease after lung resection and hilar and mediastinal node dissections. Of these 350 patients, 106 were diagnosed as having multilevel N2 disease of NSCLC by postoperative pathologic examination (Fig 1). This subgroup included 49 women and 57 men whose ages ranged from 34 to 78 years (median, 61 years).

For all patients, preoperative staging was assessed according to the TNM classification of the International Union Against Cancer [8], using chest computed tomography (CT), abdominal CT or ultrasonography, brain CT or magnetic resonance imaging, and bone scans. Clinical mediastinal and hilar lymph node status was assessed as positive if the results of the chest CT showed that the shorter axis was longer than 1.0 cm. Clinical T4 (cT4) cases and bulky N2 (shortest mediastinal lymph node diameter >2 cm) were excluded from this study because they were receiving chemotherapy with or without radiotherapy according to the protocol in our institute. Therefore, patients with mediastinal lymph node adenopathy less than 2 cm were considered for surgery. However, mediastinoscopy, fluorodeoxyglucose–positron emission tomography, or endobronchial ultrasonography-guided transbronchial needle aspiration were applied to some patients in this series (shortest mediastinal lymph node diameter ≤2 cm); they were not used for preoperative staging in this series. Furthermore, patients with extracapsular spread of lymph node metastasis were excluded, as they often underwent incomplete resections. Follow-up periods ranged from 2 to 240 months (median follow-up for living patients was 36 months).

Mediastinal nodal status was assessed according to modifications of the system by Naruke and colleagues [2], and the mediastinal nodes were classified into seven stations. These were (1) 1; (2) 2 and 3; (3) 4; (4) 5 and 6; (5) 7; (6) 8; and (7) 9. Combinations of numbers 2 and 3 and numbers 5 and 6 were included as they were difficult to separate from each other in clinical practice. When mediastinal nodal involvements were found in two or more stations, cases were classified as multilevel N2.

Patient characteristics are summarized in Table 1. The clinicopathologic records of the patients were examined for age, sex, preoperative nodal status (cN2 versus cN0 or cN1), primary tumor sites, surgical procedure, metastatic stations (distribution and numbers), tumor size, histologic features (cell type, differentiation degree, intrapulmonary metastases), presence of intrapulmonary metastases in the same lobe of the primary tumor (PM), and history of adjuvant therapies.

Survival duration was defined as the interval between surgery and either death attributable to a tumor or the most recent follow-up. Survival rates were calculated using the Kaplan-Meier method. Univariate analyses were performed using a log-rank test, χ^2 test, and logistic regression. Multivariate analyses were performed for variables with probability values less than 0.1 from univariate analysis using the logistic regression test in StatView J 5.0 (SAS Institute, Cary, NC). A probability value less than 0.05 was considered significant.

Results

Survival Rates for Patients With Multilevel N2

The postoperative 5-year survival rate for patients with multilevel N2 was 23%, and the 50% survival period was 26 months.

Table 1. Patient Characteristics

Age (y)	34–78, median age: 61
Sex (male/female)	57/49
c-N	
N0/N1/N2	50/21/35
c-T	
T1/T2/T3	40/54/12
Histologic type	
Adenocarcinoma/others	86/20
Poorly differentiated/others	31/75
Primary site	
Right: upper/middle/lower	36/7/23
Left: upper/lower	25/15
Surgical procedure	
Lobectomy/bilobectomy/ pneumonectomy	74/19/13
Adjuvant therapy	
Chemotherapy: yes/ no	35/71

Table 2. Postoperative Survival According to Clinicopathologic Factors: Univariate Analyses

Variables	5-Year Survival	*p* Value
Age		
≤ 70 (N = 86)/>70 (N = 20)	23.9%/13.0%	0.84
Sex		
Male (N = 57)/female (N = 49)	17.1%/27.5%	0.05
Tumor diameter		
<30 mm (N = 42)/>30 mm (N = 64)	24.9%/17.0%	0.66
Smoking status		
Never smoker (N = 51)/smoker (N = 55)	28.7%/16.4%	0.12
Histologic subtype		
Adenocarcinoma (N = 86)/others (N = 20)	23.8%/13.3%	0.26
Poorly differentiated (N = 31)/others (N = 75)	20.6%/22.5%	0.88
Primary tumor site		
Upper (N = 61)/others (N = 45)	26.3%/13.2%	0.41
Right (N = 66)/left (N = 40)	25.7%/14.0%	0.28
Surgical procedure		
Lobectomy (N = 74)/others (N = 32)	27.2%/12.9%	0.22
Pneumonectomy (N = 13)/others (N = 93)	8.0%/23.7%	0.37
cN		
cN0 (N = 50)/cN1–2 (N = 56)	30.0%/15.9%	0.12
cN0–1 (N = 71)/cN2 (N = 35)	26.0%/14.3%	0.03
Intrapulmonary metastasis (PM)		
Without PM (N = 77)/with PM (N = 29)	28.6%/7.2%	0.01
Metastatic mediastinal nodal stations		
2 stations (N = 57)/>2 stations (N = 49)	21.3%/22.5%	0.88
Either upper (aortic) or inferior (N = 63)/both (N = 43)	25.4%/16.2%	0.56
Adjuvant chemotherapy		
Yes (N = 35)/no (N = 71)	24.2%/21.7%	0.68
Period when surgery done		
1998–2007 (N = 44)/1988–1997 (N = 62)	15.3%/23.1%	0.52

Prognostic Factors for Multilevel N2

Univariate analyses using the variables listed in Table 2 showed that cN (cN2), PM, and sex (male) were significant adverse prognostic factors, whereas smoking status (smoker) only tended toward significance as an adverse prognostic factor ($p = 0.1$). Metastatic station (distribution and number), adjuvant therapy, the period during which surgery was done, primary tumor site, histologic subtype, tumor diameter, age, and surgical procedure were not significant prognostic factors.

By multivariate analysis ($p < 0.1$ by univariate analysis), cN (cN2) and PM were significant prognostic factors (Table 3).

Survival Rate According to the Prognostic Factors for Multilevel N2

The multilevel N2 patients were categorized as with or without significant prognostic factors determined from multivariate analyses. Patients who had neither cN2 nor PM showed a significantly higher survival rate than patients who had either cN2 or PM (5-year survival rates of 36.5% and 11.2%, respectively; Fig 2).

Table 3. Prognostic Factors for Patients With Multilevel N2: Multivariate Analysis Model 1

Variables	Odds Ratio	95% CI	*p* Value
Sex (female)	0.62	0.34–1.14	0.12
Smoking status (smoker)	0.98	0.54–1.78	0.98
cN (N2)	1.61	1.01–2.58	0.04
PM (positive)	1.99	1.21–3.26	0.007

CI = confidence interval; PM = intrapulmonary metastases.

Comment

It is well known that patients who have NSCLC with ipsilateral mediastinal lymph node (N2) involvement are a heterogeneous group [9–12]. This heterogeneity involves multiple factors, such as preoperative detection, susceptibility to neoadjuvant treatment, clinically unsuspected N2 disease, and the level or site and number, or both, of mediastinal lymph nodes that are involved [13, 14]. Examples of factors to be considered include cN2 prognosis worse than the respective unsuspected pN2, single versus different multiple N2 stations, the number of involved lymph nodes, extracapsular spread, the presence of subcarinal node metastasis, and skip metastasis [15, 16]. Each of these subclassifications should be considered as a completely different subpopulation of positive mediastinal lymph nodes.

It has been shown that multilevel N2 patients have much poorer prognoses than those with single-level N2. Thus, there have been few studies that have considered prognostic factors for multilevel N2. Recently, the numbers of pathologically proven multilevel N2 cases before surgery have been increasing owing to the use of new diagnostic modalities, such as endobronchial ultrasonography-guided transbronchial needle aspiration. Further-

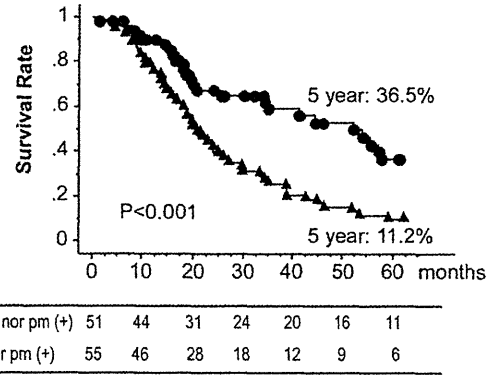

Fig 2. Overall 5-year survival rate for multilevel N2 patients (Pt) depends on cN and intrapulmonary metastases (pm). Survival curves were generated using the Kaplan-Meier method.

more, this multilevel N2 subpopulation of patients without mediastinal lymphadenopathy has been increasing. However, the impact of clinical N status on prognosis for multilevel N2 has been unclear.

We have demonstrated that cN2 and PM are important, poor-prognosis factors for multilevel N2 patients. The 5-year survival for cN0 multilevel N2 patients (N = 50) was much better than that of cN2 multilevel N2 patients (30.0% and 14.3%, respectively). In contrast, the numbers of metastatic stations or the distributions of metastatic stations were not prognostic factors for multilevel N2. Previous reports have shown that for patients with mediastinal lymph node metastases, cN2 was highly associated with unexpected N3, which would not be detected preoperatively by routine evaluations.

That is, for patients with mediastinal nodal involvement, more than 70% of patients with cN2 had unexpected N3, resulting in a poor prognosis. However, less than 20% of patients with cN0 or cN1 had unexpected N3 [4, 12]. Furthermore, it is well known that the prognosis for occult N2 metastasis is better than that for patients with clinical N2 disease after surgical resection [13]. Thus, clinical N status evaluated by CT (size criteria) was associated with prognosis, even for multilevel N2 patients.

Because we excluded bulky cN2 from an indication for surgery, and multilevel cN2 cases were also excluded from indications for surgery during the study period, 70% of multilevel N2 was diagnosed as cN0 or cN1 during preoperative examination using CT. Thus, more than a few patients without adenopathy must exist in the multilevel N2 population. Therefore, it is important for us to recognize the difference in prognosis between cN0 or cN1 and cN2 in multilevel N2.

Intrapulmonary metastasis within the same lobe of the primary tumor is an established poor prognostic factor and is classified as T4. The incidence of PM has been reported to be 8% to 9% in NSCLC patients who underwent resection [17, 18]. The incidence of PM according to nodal status was 3.7% in N0, 7.6% in N1, and 14.8% in N2 [17]. The incidence of PM was 27.4% in this series, and that result is compatible with the idea that multilevel N2 is a more advanced stage than single-level N2. Furthermore, PM was an adverse prognostic factor even for multilevel N2 patients. Therefore, PM should be taken into consideration as an important negative factor affecting prognosis when evaluating therapeutic strategies in multilevel N2 patients.

Limitations of the present study include the retrospective nature of the analysis and that routine adjuvant chemotherapy for N2 patients was started in 2006. Therefore, it was difficult to evaluate the effect of adjuvant chemotherapy on prognosis in this study.

In conclusion, multilevel N2 patients can be grouped according to their prognoses by the factors cN and PM. These findings have potential for analyzing the best therapeutic modalities for multilevel N2 patients.

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Salvage surgery for advanced non–small cell lung cancer after response to gefitinib

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (EGFR-TKI) gefitinib has dramatic efficacy in more than 70% of advanced non–small cell lung cancers with EGFR gene mutations.[1] Some patients with inoperable systemic non–small cell lung cancers demonstrate a downstaging of their cancer to operable disease status after gefitinib treatment. Despite high response rates for EGFR mutant tumors, the median time to progression is about 1 year.[1] The EGFR T790M mutation and *MET* amplification are thought to be the underlying mechanisms of the acquired resistance to EGFR-TKIs. When complete resection of residual disease is possible, the patients can then be considered disease free. We have aggressively performed salvage lung resections for patients with gefitinib responses and demonstrated downstaging to N0M0. The purpose of this study was to assess

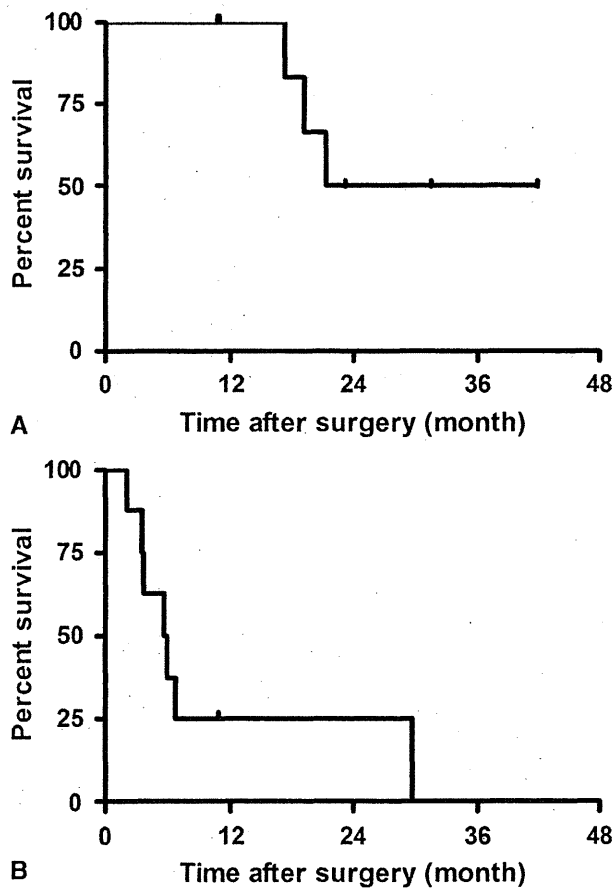

FIGURE 1. A, Overall survival curve of patients who underwent surgical resection after response to gefitinib administration. Median overall survival after surgery was 32 months. B, Recurrence-free survival curve of patients who underwent surgical resection after response to gefitinib administration. Median recurrence-free survival after surgery was 6 months.

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TABLE 1. Patient characteristics

Case	Age (y), sex	Initial CS	Treatment before gefitinib (response)	Gefitinib duration	CS before surgery
1	73, F	cT4(PM)N2M0, IIIB	None	3 mo	cT2N0M0, IB
2	51, F	cT2N3M1(brain), IV	None	3 y	cT1N0M0, IA (local regrowth)
3	58, F	cT2N2M0, IIIA	CDDP+VNR (SD), CBDCA+PTX (SD)	5 mo	cT1N0M0, IA
4	58, F	cT4(D+)N0M0, IIIB	CDDP+GEM (SD)	2 y, 10 mo	cT1N0M0, IA (local regrowth)
5	63, F	cT2N3M1(abd LN), IV	CDDP+TS-1 (PR)	1 y, 4 mo	cT1N0M0, IA (local regrowth)
6	33, M	cT4 (PM, E+)N0M0, IIIB	CBDCA+PTX (SD)	2 mo	cT1N0M0, IA
7	54, M	cT4N3M1(PM), IV	CDDP+DTX (SD)	1 y, 10 mo	cT1N0M0, IA
8	71, F	cT2N3M0, IIIB	None	1 y, 6 mo	cT2N0M0, IB
9	57, F	cT4N0M1(PM), IV	CBDCA+DTX (SD)	Unknown	cT1N0M0, IA

CS, Clinical stage; *EGFR*, epidermal growth factor receptor; *PM*, pulmonary metastasis; *DWD*, died with disease; *AWD*, alive with disease; *CDDP*, cisplatin; *VNR*, vinorelbine tartrate; *SD*, stable disease; *CBDCA*, carboplatin; *PTX*, paclitaxel; *CR*, complete response; *D*, pleural dissemination; *GEM*, gemcitabine; *AWOD*, alive without disease; *abd LN*, abdominal lymph node; *TS-1*, tegafur/gimeracil/oteracil potassium; *PR*, partial response; *E*, malignant pleural effusion; *DTX*, docetaxel. *. Endothelial growth factor receptor mutational analysis was performed on pretreatment biopsy specimens obtained by bronchoscopy.

the perioperative safety and survival benefit of these salvage lung resections.

CLINICAL SUMMARY

After institutional review board approval at each institution, the clinicopathologic profiles of a total of 9 patients were collected by a questionnaire survey in 2009 from 7 institutions belonging to the Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group. The questionnaire included the following items: sex, age, smoking history, clinical (pretreatment) stage, response to therapy before gefitinib monotherapy, response to and adverse effects of gefitinib monotherapy, duration of gefitinib administration, withdrawal period of gefitinib before surgery, preoperative clinical stage, surgical procedure, morbidity and mortality of surgery, primary site by lobe, histology, pathologic stage, EGFR mutation status, postoperative therapy, survival time, recurrence, and cause of death.

The patient characteristics are shown in Table 1. All cases were adenocarcinoma, and all had been initially diagnosed as inoperable. Surgery was performed to eradicate residual tumors or local recurrence and regrowth, with a median administration period of 17 months (range, 2–36 months). Gefitinib was terminated before surgery in all cases, with a median withdrawal period of 7 days (range, 1–21 days). Resection was accomplished in all cases, with a median hospital stay of 9 days (range, 6–34 days). There was 1 case of mild liver dysfunction, and there were no deaths. An EGFR mutational analysis of resected specimens or of the pretreatment biopsy specimen (patient 3) was performed in 7 cases. Six of 7 patients harbored EGFR mutations, exon 19 deletions or exon 21 L858R. Two patients also had EGFR-TKI–resistant exon 20 T790M mutations. Four patients who underwent surgery in late study period received gefitinib postoperatively for various durations. Despite the remarkable downstaging of the patients' disease after gefitinib treatment, 7 of 9 patients showed a more advanced pathologic stage than their preoperative clinical stage. Six patients with initial N2-3 disease all had radiologic downstaging to N0 status before attempted resection. Pathologically, 2 patients had persistent N2 disease and 1 had N1 disease. The recurrence-free and overall survivals are shown in Figure 1 (*A* and *B*). The most common site of recurrence was the brain. One patient has been alive without disease for 11 months with the use of adjuvant gefitinib.

DISCUSSION

Our patient population had no serious immediate postoperative morbidity or mortality. Among a total of 41 patients in the literature who underwent lung resection after EGFR-TKI treatment, none died perioperatively.[2-5] Although there has been some concern that preoperative EGFR-TKIs may be associated with impaired wound healing, major lung resection after EGFR-TKI therapy may be feasible.

On the other hand, postoperative survival in the this series was not satisfactory, with a median recurrence-free survival of 6 months. Despite dramatic radiographic downstaging after gefitinib treatment, 7 of 9 patients had further advanced pathologic stages than their preoperative clinical stages. Dramatic radiologic response does not necessarily correlate with cell death. Our results suggest that initially expressed systemic disease was essentially unchanged even after dramatic radiologic response to gefitinib. Surgery after gefitinib treatment should be limited to patients without initial evidence of disseminated and distant metastases. EGFR-TKIs have both higher and more rapid responses, and better toxicity profiles than standard chemotherapy for non–small cell lung cancers harboring EGFR mutation. Preoperative EGFR-TKI treatment strategy should be reevaluated in the neoadjuvant setting for early to locally advanced but operable disease. The optimal duration of EGFR-TKI treatment,

TABLE 1. Continued

Mode of resection	Pathologic stage	EGFR gene status	Adjuvant therapy	Outcome
Lobectomy	pT2N1M0, IIB	Wild type	None	Bone metastasis (6 mo), DWD (1 y, 5 mo)
Lobectomy	pT1N0M0, IA	Exon 19 (del)	None	Brain metastasis (2 mo), AWD (3 y, 6 mo)
Left pneumonectomy	Pathologic CR	Exon 19 (del)*	Gefitinib (2 y)	Brain metastasis (2 y, 4 mo), AWD (2 y, 7 mo)
Bilobectomy	pT1N1M0, IIA	Exon 19 (del)	Gefitinib (11 mo)	AWOD (11 mo)
Lobectomy	pT1N2M0, IIIA	Unknown	None	Brain metastasis (5 mo), AWD (2 y)
Left extrapleural pneumonectomy	pT4N2M0, IIIB	Exon 19 (del)	Gefitinib (3 mo)	Brain metastasis (3 mo), DWD (1 y, 7 mo)
Lobectomy	pT4N0M0, IIIB	Exon 19 (del) Exon 20 (T790M)	None	Metastasis in thorax (6 mo), AWD (10 mo)
Lobectomy	pT2N2M0, IIIA	Exon 21 (L858R) Exon 20 (T790M)	None	Metastasis in thorax (4 mo), DWD (1 y, 9 mo)
Lobectomy	pT2N0M0, IB	Unknown	Gefitinib	Unknown

the timing of surgery, and the role of adjuvant EGFR-TKI treatment should be also investigated in the future.

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Aortic dissection and rupture in adolescents after tetralogy of Fallot repair

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Aortic dissection in children and adolescents is rare, yet it is associated with high mortality. A recent article[1] describing 13 patients with aortic dissections operated between 1970 and 2000 reported an operative mortality of 38%. Progressive aortic root dilatation is a recognized feature of tetralogy of Fallot (TOF)[2,3] and generally managed conservatively. However, 2 recent reports of aortic dissection in patients with aortic aneurysm after TOF repair[4,5] together with the case presented reemphasize the fact that aortic root dilatation must be monitored closely in patients with TOF.

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Institutional report - Thoracic oncologic

Outcome of surgical resection of pulmonary metastasis from urinary tract transitional cell carcinoma

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Abstract

There is little information on pulmonary metastasectomy of urinary tract transitional cell carcinoma (TCC). In this study, we examined the long-term outcome and the factors associated with long-term survival after pulmonary metastasectomy of urinary tract TCC based on a 20-year single center experience. Between 1984 and 2005, 18 patients (12 men, six women) underwent pulmonary metastasectomy of the urinary tract TCC in our hospital. The clinicopathological and surgical data of these patients obtained from the medical records were analyzed in this retrospective study. The time interval between lung resection and death, or latest follow-up ranged from two to 200 months (median 52). Survival analysis was conducted by the Kaplan–Meier method and log-rank test. The cumulative three- and five-year survival rates were 59.8% and 46.5%, respectively. The number of resected metastatic tumors (solitary vs. multiple) was associated with long-term survival ($P<0.05$). The five-year survival rate of patients with solitary metastasis was 85.7% while that of patients with multiple metastases was 20.0%. Pulmonary metastasectomy of urinary tract TCC is associated with a favorable outcome, and solitary metastasis is associated with long-term survival. Aggressive management of solitary pulmonary metastasis from a urinary tract TCC is feasible in selected patients.

Keywords: Urothelial cancer; Lung; Metastasectomy

1. Introduction

Systemic chemotherapy remains the standard treatment for metastatic transitional cell carcinoma (TCC) of the urinary tract [1]. Modern cisplatin-based combination chemotherapy regimens introduced in the 1980s have been reported to be associated with overall response rates of 50–70% [2, 3]. Although cisplatin-based chemotherapy is highly effective initially, long-term survival is achieved in only a small proportion of patients. New treatment options, such as target therapies have been investigated [4]. Despite these efforts, metastatic TCC is still associated with poor prognosis.

Several groups have reported the surgical results of metastatic TCC including those in different locations in selected patients. In 1939, Barney and Churchill were the first to describe successful pulmonary metastasectomy [5]. It is now thought that surgical resection of pulmonary metastasis is an established treatment modality in patients with various types of metastatic diseases, such as colorectal cancer, osteosarcoma, and soft tissue sarcoma [6]. However, little is known about surgical resection of pulmonary metastasis from a urinary tract TCC. Because patients with pulmonary metastasis of urinary tract TCC have poor prognosis, surgical resection is rarely applied. To our knowledge, there is little information on the significance and prognosis of patients who undergo resection of pulmonary metastatic lesions from urinary tract TCC.

In this retrospective study, we examined the long-term results, and factors associated with prolonged survival after pulmonary metastasectomy of urinary tract TCC based on a 20-year single center experience.

2. Patients and methods

In our hospital, lung resection is considered for patients with pulmonary metastasis of urinary tract TCC when the patient meets the following criteria. (1) Pulmonary metastases are deemed completely respectable and mediastinal or hilar lymph nodes are not involved by preoperative radiological studies. Generally, mediastinal or lymph node involvement is assessed by contrast-enhanced CT. Lymph nodes were interpreted as positive if >1 cm across the short-axis diameter. (2) Metastatic disease is limited to the lungs. (3) Locoregional control of the primary cancer was achieved or achievable. (4) Good overall general conditions and adequate respiratory function to tolerate lung resection.

According to the eligibility criteria described above, 18 patients (12 men, six women) underwent pulmonary metastasectomy of the urinary tract TCC in our hospital between 1984 and 2005. A retrospective analysis of these 18 patients

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was performed. Histopathological evaluation of the resected specimens of the lung confirmed urinary tract TCC metastases in all patients. Clinical information was obtained from the medical records of our hospital.

The primary sites were the bladder in nine patients, the upper urinary tract in six patients, and multiple tumors in both the bladder and upper urinary tract in three patients. Of nine patients with bladder cancer, one patient underwent transurethral resection of the bladder tumor (TUR-Bt), and eight patients underwent cystectomy. All six patients with renal pelvis or ureter cancer underwent nephroureterectomy. Of three patients with multiple tumors in both the bladder and renal pelvis or ureter, one patient underwent nephroureterectomy and cystectomy while two patients underwent nephroureterectomy and TUR-Bt. Seventeen patients underwent surgery alone as initial therapy for the primary tumor. One patient underwent simultaneous resection of the primary cancer and pulmonary metastasis. The mean and median time interval between resection of the primary urinary tract TCC and lung resection was 37 and 24 months, respectively (range: 0–126 months). The mean patient age at the time of metastasectomy was 66 years (range: 44–84 years). None of the patients had a history of resection of extrapulmonary metastases. Eight of the 18 patients including one patient who underwent simultaneous resection of the primary cancer and pulmonary metastasis received preoperative or postoperative cisplatin-based chemotherapy or both. Five patients received methotrexate, epirubicin, and cisplatin (MEC) chemotherapy preoperatively, and partial response (PR) was observed in four and no response in one. One patient received preoperative MEC and postoperative gemcitabine, cisplatin (GC), while another received preoperative methotrexate, vinblastine, adriamycin and cisplatin (M-VAC), and PR was observed in these two patients. One patient received postoperative MEC chemotherapy without any preoperative chemotherapy. The response to chemotherapy was assessed using the criteria described in a previous study [7]. Table 1 summarizes the clinicopathological characteristics of the patients.

The disease-free interval (DFI) was defined as the time period from surgical resection of primary cancer to the initial diagnosis of pulmonary metastasis. The criteria used for complete resection were the following: lack of other extrapulmonary metastases, no locoregional recurrence, and no macroscopic tumor tissue is left behind at lung resection.

Follow-up was generally based on chest X-ray or chest and abdominal CT, physical examination and laboratory blood tests performed every six to 12 months after lung resection. The follow-up information was obtained from the hospital medical records, the corresponding urological departments, letters from the general practitioners, or from the death certificates of the registry office. Patients or their families were contacted by phone if necessary. Overall survival was the main endpoint defined as the time interval between the date of lung resection and death, or the last follow-up for living patients. The time interval between lung resection and death, or latest follow-up in the present series ranged from two to 200 months (median 52).

Table 1
Patients' characteristics

Characteristics	Number of patients
Sex	
Male	12
Female	6
Age (years)	
Mean	66
Range	44–84
Primary site	
Urinary bladder	9
Renal pelvis or ureter	6
Multiple tumor in both bladder and renal pelvis or ureter	3
Pathological stage of primary TCC*	
0a,0is,I	5
II	3
III	5
IV	2
Unknown	3
Histopathological grading of primary TCC	
G1	1
G2	10
G3	4
Unknown	3
Perioperative chemotherapy for lung metastasis	
Yes	8
Preoperative MEC	5
Preoperative MEC and postoperative GC	1
Preoperative M-VAC and postoperative MEC	1
Postoperative MEC	1
No	8
Unknown	2
Time interval between primary resection and lung resection (months)	
<12	3
12–24	6
24–60	6
≥60	3

*Stage of disease was defined according to the 1997 update of TNM criteria established by UICC.

TCC, transitional cell carcinoma; MEC, methotrexate, epirubicin, and cisplatin; GC, gemcitabine, cisplatin; M-VAC, methotrexate, vinblastine, adriamycin and cisplatin.

All statistical analyses were conducted using StatView 5.0 software (SAS Institute, Berkley, CA, USA). Overall survival was analyzed by the Kaplan–Meier method using the date of pulmonary resection as the starting point. The significance of differences between groups was analyzed by the log-rank test. A $P<0.05$ was considered statistically significant.

3. Results

Complete resection was achieved in 16 patients (89%). There was no operative mortality. Two patients (11%) developed postoperative complications, including wound infection in one patient and pyothorax in another. Table 2 provides details on the metastatic tumors and lung resection. We excluded the patients with apparent hilar or mediastinal lymph node metastases determined by preoperative radiological examinations from candidate for pulmonary resection, however, two patients revealed to have hilar or mediastinal lymph node metastases pathologically after the operation. Three patients underwent repeat lung

Table 2
Pathological details of lung resection

Factors	Number of patients
Number of resected metastases*	
1	8
2	6
≥3	4
Largest size of metastases (cm)	
<3	9
≥3	9
Type of resection	
Sublobar resection	14
Lobectomy	4
Hilar or mediastinal lymph node metastasis	
Yes	2
No	4
Lymph node sampling was not done	12
Completeness of resection	
Complete resection	16
Incomplete resection	2

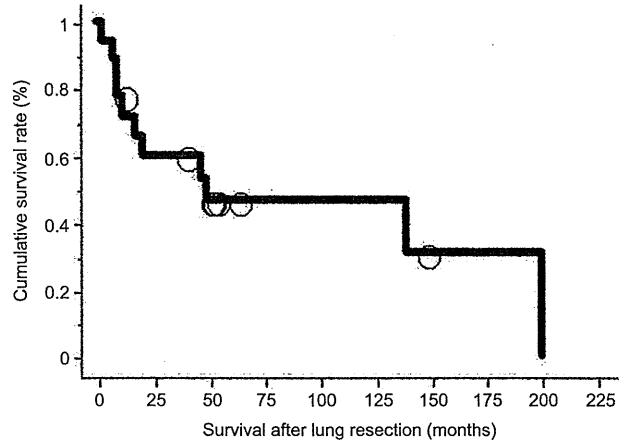

Fig. 1. Overall survival rates of 18 patients. The cumulative three- and five-year survival rates were 59.8% and 46.5%, respectively. Circles: censored cases.

resection due to metachronous pulmonary metastasis of urinary tract TCC.

Two patients who developed recurrences after lung resection were lost to follow-up. Eleven patients died of the disease, two patients are still alive with the disease, and three patients are alive with no evidence of disease (NED). All three patients who are alive with NED are long survivors, >48 months. Details of these three patients are listed in Table 3. The sites of recurrences after lung resection were the lung in five patients, bone in five patients, brain in two patients, urinary system in two patients, and unknown in one patient. The cumulative three- and five-year survival rates were 59.8% and 46.5%, respectively (Fig. 1).

The following factors were assessed by univariate analysis for their association with long-term survival; sex, age, primary site, pathological stage of the primary urinary tract TCC according to TNM classification, histological grading of the primary urinary tract TCC, perioperative chemotherapy before/after lung resection, DFI, number of lung metastatic tumors, diameter of the largest resected lung metastases, type of resection (lobectomy or sublobar resection), presence of hilar or mediastinal lymph node metastasis, and completeness of resection. The results of univariate analysis are shown in Table 4. The number of resected metastatic tumors (solitary vs. multiple) was significantly associated with long-term survival ($P<0.05$). The five-year survival rate of patients with solitary metastasis was 85.7% while that of patients with multiple metastases was 20.0%.

Table 4
Results of univariate analysis

Factors	*P*-value
Sex	NS
Age (<70 years vs. ≥70 years)	NS
Primary site	NS
Pathological stage of primary TCC (0a,0is,I, II vs. III, IV)	NS
Histological grade of primary TCC (G1,2 vs. G3)	NS
Use of perioperative chemotherapy for lung resection	NS
Disease-free interval (<24 months vs. ≥24 months)	NS
Number of resected metastatic tumors (solitary vs. multiple)	0.009
Largest size of metastatic tumor (<3 cm vs. ≥3 cm)	NS
Type of resection (sublobar resection vs. lobectomy)	NS
Hilar or mediastinal lymph node metastasis (yes vs. no)	NS
Completeness of resection (complete vs. incomplete)	NS

NS, not significant; TCC, transitional cell carcinoma.

Fig. 2 depicts the survival curve according to the number of resected metastases.

4. Discussion

In our hospital, a total of 780 pulmonary metastasectomies have been performed for various diseases, such as colorectal cancer, soft tissue sarcoma, hepatocellular carcinoma according to the general eligibility criteria described in Patients and methods [8]. In this study, we analyzed pulmonary metastasectomy of the urinary tract TCC, with a

Table 3
Details of long survivors without disease

Case	Age (years)	Primary site	Stage of primary tumor	Number of metastasis	Size of tumor (mm)	Chemotherapy (response)	DFI (months)	Outcome (months after resection)
1	57	Renal pelvis	4	1	33	Not administered	12	51, NED
2	78	Ureter	3	1	20	Not administered	22	54, NED
3	48	Ureter	1	2	12	Preoperative MEC (PR) and postoperative GC	59	69, NED

All patients were males and the histological grade was G2 in all three patients.
DFI, disease free interval; NED, no evidence of disease; MEC, methotrexate, epirubicin, and cisplatin; PR, partial response; GC, gemcitabine and cisplatin.

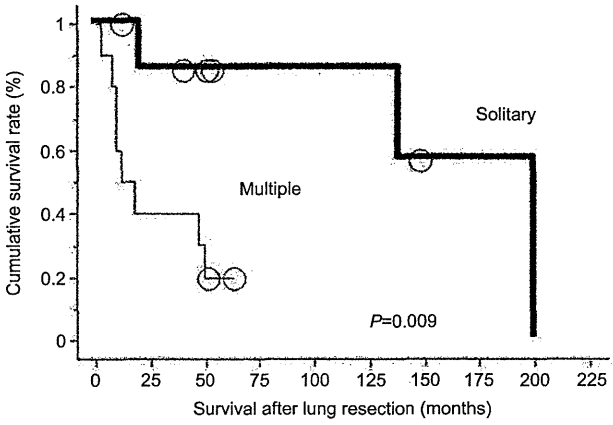

Fig. 2. Probability of survival of patients with solitary metastasis compared with that of patients with multiple metastases. Circles: censored cases.

special emphasis on the long-term outcome and the factors associated with prognosis.

According to the guidelines, systemic chemotherapy is the standard treatment for metastatic urinary tract TCC [1, 9]. When the tumor responds well to the chemotherapy, aggressive surgical approach is encouraged. However, when the disease is refractory to chemotherapy, the indication for metastasectomy is limited to symptomatic patients. Metastasectomy without chemotherapy is not usually recommended, however, there is no clear evidence against metastasectomy without chemotherapy.

In 1982, Cowles and colleagues [10] were the first group to report the surgical outcome of pulmonary metastasis of urinary tract TCC. They reported a median survival of five years for six patients following surgical resection for solitary pulmonary metastasis of urinary tract TCC without chemotherapy. A decade after that report, based on the development of modern cisplatin-based combination chemotherapy regimens [2], aggressive surgical resection of metastatic TCC that responds well to chemotherapy is encouraged by some authors [7, 11]. However, the majority of patients in the above studies had locally advanced disease or metastatic pelvic lymph nodes, while only a few had pulmonary metastasis. Otto et al. [12] examined surgical results of metastatic TCC refractory to chemotherapy and concluded that the indication for metastasectomy was limited to symptomatic patients because no survival benefit was confirmed in this cohort. Siefker-Radtke et al. [13] reported a heterogeneous group of 31 patients with distant metastatic TCC. Their series included 24 patients with pulmonary metastasis, which is the largest number of cases treated by pulmonary metastasectomy. Nine of their 31 patients underwent metastasectomy without chemotherapy. The median overall survival time was 23 months with a five-year survival rate of 33%. Recently, Abe and co-workers [14] and Lehmann et al. [15] reported the surgical results of two heterogeneous groups of patients with distant metastatic TCC with a median overall survival of 28 months and 42 months, respectively.

In the present study, the cumulative three- and five-year overall survival rates for pulmonary metastasectomy were 59.8% and 46.5%, respectively. It is difficult to compare our results with those of previous studies with a five-year overall survival rate ranging from 27 to 33% [13, 15], because of the heterogeneous metastatic sites of the patients reported in the previous studies. One possibility that could explain this difference is that pulmonary metastasectomy contributes to better outcome than metastasectomy of other sites, such as retroperitoneal lymph nodes, distant lymph nodes, brain, skin, and bone.

Neither the site of the primary tumor nor the surgical mode for the primary tumor affected survival in the present study. Because only one patient received perioperative chemotherapy as an initial treatment for the primary tumor (the patient underwent simultaneous resection of the primary cancer and pulmonary metastasis received preoperative MEC chemotherapy), the effect of chemotherapy as initial treatment for primary tumor cannot be assessed. In the present study, similar to the report of Siefker-Radtke et al. [13], neither chemotherapy nor the response status to such therapy affected survival. In fact, two of the three long-term survivors without disease in our series underwent surgery alone. Lehmann et al. [15] also reported two long-term survivors who never received chemotherapy. Initial treatment for the primary tumor also does not affect survival in the present study. Based on these data, we conclude that surgical resection is one of the useful treatment for a subgroup of patients with pulmonary metastasis of urinary tract TCC.

The present study identified solitary metastasis as a factor associated with prolonged survival after pulmonary metastasectomy. To our knowledge, this is the first study that identified this factor to be associated with prolonged survival after pulmonary metastasectomy of the urinary tract TCC. Siefker-Radtke et al. [13] reported that age, gender, race, primary site, duration of chemotherapy after the diagnosis of metastases before resection and pathology of the primary tumor or metastases did not influence survival in their series, although the number of metastatic tumors was not assessed in their report. In the present study, the survival of patients with solitary metastasis was quite good. These data are in agreement with the first report on the surgical results of pulmonary metastasis of the urinary tract TCC by Cowles et al. [10].

The limitation of this study is the small number of patients. Accordingly, it is difficult to define the significant prognostic factors using multivariate analysis. Furthermore, a longer follow-up period is needed to determine the true recurrence rate in the long-term survivors.

5. Conclusions

Surgical resection of pulmonary metastasis of urinary tract TCC provides favorable long-term outcome in selected patients. Solitary metastasis was associated with long-term survival after pulmonary metastasectomy. Aggressive management of patients with solitary pulmonary metastasis from urinary tract TCC is feasible in selected patients.

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Sublobar Resection Provides an Equivalent Survival After Lobectomy in Elderly Patients With Early Lung Cancer

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Background. Sublobar resection is indicated for early-stage non-small cell lung cancer in patients with a perioperative risk associated with impaired medical conditions. This study was conducted to investigate the clinical impact of this procedure in the elderly.

Methods. The patients who underwent complete resection for stage IA non-small cell lung cancer from 1990 and 2007 were enrolled (n = 764). Two age groups were defined as elderly (≥75 years) and younger (<75 years) patients. The 5-year survival, recurrence, and postoperative complications after sublobar resection were compared with those after standard lobectomy according to age group.

Results. There were 133 elderly patients (79 standard lobectomies and 54 sublobar resections) and 631 younger patients (539 standard lobectomies and 92 sublobar resections). While the 5-year survival after sublobar resection was significantly inferior to that after standard lobectomy in the younger group (64.0% and 90.9%, respectively, $p < 0.0001$), however, no substantial difference was observed in the elderly (67.6% and 74.3%, $p = 0.92$). Locoregional recurrence rates were higher in patients after sublobar resection than those after standard lobectomy in both the elderly (11.1% vs 1.3%) and the younger (12.0% vs 1.5%) groups. No significant difference in postoperative complications was observed between the types of surgery in the elderly.

Conclusions. Sublobar resection for stage IA is considered to be an appropriate treatment in the elderly patients as this procedure provides an equivalent long-term outcome in comparison with lobectomy. A larger scale study with matching patients is necessary to confirm the noninferiority of sublobar resection in comparison with standard lobectomy in this population.

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Lung cancer is the leading cause of cancer-related deaths in many countries and patients older than 80 years account for 14% of all lung cancers [1, 2]. The number of elderly lung cancer patients is increasing rapidly worldwide. Comorbid illness and adverse medical conditions due to aging is a significant concern to treat elderly patients with lung cancer [3]. Lobectomy is the current standard treatment for early-stage non-small cell lung cancer (NSCLC) in the general population. Sublobar resection such as wedge resection and segmentectomy could be indicated in patients with stage I NSCLC, who may tolerate operative intervention but not a lobar or greater lung resection because of comorbid disease or decreased cardiopulmonary function [4]. When treating elderly patients, decisions regarding the treatment strategy, lobectomy, or sublobar resection, must therefore carefully balance the risks of postsurgical morbidity and mortality with those affecting cancer recurrence and long-term survival.

This study was conducted to investigate the clinical impact of sublobar resection in the elderly patients in comparison with their younger counterparts. The short-term and long-term outcomes after sublobar resection for stage IA NSCLC were compared with those after standard lobectomy according to the age group.

Patients and Methods

Patients

This study conducted a retrospective review of 984 patients who underwent complete resection for stage IA NSCLC at the Osaka Medical Center for Cancer and Cardiovascular Diseases from January 1991 to December 2007. The ethics committee gave its approval for the publication of this retrospective study with a waiver of informed consent (N0.1003175124) from the individual patients. The institutional prospective database of the general thoracic department included clinicopathologic variables and the postoperative clinical course. The pri-

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mary variables were gender, age, smoking status, preoperative treatment, comorbidity, surgical procedure, curability, diameter of surgical tumor specimen, histology, and pathologic (p) stage. The outcomes included postoperative complications, type of recurrence, and survival time. The type of surgery was categorized into two groups according to the extent of the pulmonary resection; standard surgery including a lobar or greater lung resection and sublobar resection such as segmentectomy and wedge resection. Any patients undergoing sublobar resections with a radical intent for the treatment of small-sized (2 cm or smaller) noninvasive carcinoma (n = 220) were excluded from the study. Definition of radical intent sublobar resection was described in detail in the previous report [5]. Briefly, the indications for radical intent sublobar resection were determined according to the diameter of the nodule and the percentage of ground-glass opacity on high-resolution computed tomographic (CT) scans. Finally, 618 patients who had standard surgery and 146 patients who underwent sublobar resection were enrolled in the study. Two age groups were defined as elderly (≥75 years) and younger (<75 years) patients.

Preoperative and Intraoperative Evaluation and Staging

The preoperative evaluation included a detailed clinical history and physical examination, chest radiography, chest and upper abdominal CT scans, brain magnetic resonance imaging, and bone scintigraphy or fluorodeoxyglucose-positron emission tomography scan for staging and assessment of respectability. All patients were staged intraoperatively and pathologically according to the sixth TNM (tumor-nodes-metastasis) classification at the time of surgery, and the TNM descriptions were converted to the seventh edition which has been recently updated [6]. Hilar and (or) mediastinal lymph nodes were sampled or systematically dissected during lobectomy or segmentectomy to evaluate for the possibility of occult nodal metastases. On the other hand, only swollen nodes were sampled in the patients who underwent wedge resection. A lavage cytologic examination was routinely used to assess the resection margins for tumor presence intraoperatively, as previously reported [7].

Reasons for Selecting Sublobar Resection and Postoperative Complications

Comorbid diseases and postoperative complications were diagnosed by laboratory, radiologic, and physiologic examinations. The reasons for selecting sublobar resection were defined as the following: insufficient pulmonary function or chronic lung diseases (abnormal spirometry test and [or] apparent interstitial shadow or emphysema detected by chest CT); insufficient cardiac function or cardiovascular diseases; previous lung surgery (greater than lobectomy) or active multiple lung cancer; cancer history; and diabetes mellitus. Multiple reasons were allowed. Complications were defined as the following: life-threatening complications which required any kind of emergent interventional treatment, or transfer to an intensive care unit; major complications were those that were potentially life threatening but did not require emergency intervention; and minor complications included those that required therapy and a prolonged hospital stay.

Recurrence of the Disease and Survival

Recurrence was diagnosed by daily clinical practice and defined as locoregional if it occurred within the same lobe, the mediastinal lymph nodes, or the hilum. All other types of recurrence were categorized as distant recurrence. The survival time was measured from the date of surgery to the date of the most recent follow-up examination or the date of death. The patients lost to the follow-up within ten years after surgery were censored at the date of last contact with the institution.

Statistical Analysis

The χ^2 test or Fisher exact test was used to compare the frequencies of categoric measures. Survival was calculated by the Kaplan-Meier method and differences in survival were assessed by a log-rank analysis. To adjust the effect of death due to other causes and to control the difference in the age and gender distribution between the sublobar resection group and the standard surgery, we calculated the relative survival and performed an age stratified analysis. The relative survival was estimated using the maximum-likelihood approach for individual data with the publicly available STATA program *strel* (StataCorp, College Station, TX) [8, 9]. The relative survival was the ratio of the observed survival rate in the patient group and the expected survival rate derived from the population life tables after matching for the age, calendar year, and sex. It can be interpreted as the survival from cancer after adjustment for other causes of deaths. A multivariate analysis for prognostic factors was performed using the Cox proportional hazard regression model. The p values less than 0.05 were considered to be statistically significant.

Results

Patient Characteristics

Table 1 summarizes the patient characteristics from the age groups. The tumor histology was as follows: adenocarcinoma in 637 patients; squamous cell carcinoma in 105; large cell carcinoma in 11; adenosquamous carcinoma in 8; and 3 pleomorphic or sarcomatoid carcinoma. The standard surgery group in the total cohort included 2 pneumonectomies, 12 bilobectomies, and 604 lobectomies, while the sublobar resection group included 90 segmentectomies and 56 wedge resections. There were more males ($p = 0.0189$), more squamous cell carcinomas ($p = 0.001$), and more ex-smokers or current smokers ($p < 0.0001$) in comparison with those in the standard lobectomy group. The histology and smoking status were significantly different between the types of surgery in the elderly patients (≥75 years of age). All of the patients had macroscopically negative surgical margin. Operative mortalities, which included deaths within the first 30

Table 1. Patients' Characteristics From the Overall Cohort and Each Age Group

	Younger (<75 Years)			Elderly (≥75 Years)		
Characteristic	Standard (n = 539)	Sublobar (n = 92)	*p* Value	Standard (n = 79)	Sublobar (n = 54)	*p* Value
Age (years)						
Median (mean)	64	68		77	78	
Range	35–74	38–74	<0.0001	75–87	75–84	0.2080
Gender						
Male	258	72	0.0189	45	39	0.1074
Female	281	20		34	15	
T stage						
T1a (≤20 mm)	198	46	0.1885	25	22	0.4976
T1b (>20 mm)	341	46		54	32	
Histology						
Adenocarcinoma	468	67	0.0010	66	36	0.0400
Squamous cell carcinoma	59	19		10	17	
Others	12	6		3	1	
Surgery						
Pneumonectomy	2	0	NA	0	0	NA
Lobectomy	537	0		82	0	
Segmentectomy	0	57		0	33	
Wedge	0	35		0	21	
Smoking status						
Ex- or current smoker	256	65	<0.0001	44	40	0.0481

NA = not applicable.

days after surgery or during the same hospitalization, were not recorded in this study.

Reasons for Selecting Sublobar Resection

The reasons for selecting sublobar resection are listed in Table 2. Insufficient pulmonary function or chronic lung disease was the most common and insufficient cardiac function or cardiovascular disease was the second. All of the patients with cancer history were examined thoroughly before pulmonary resection to confirm that they had no active recurrence or metastatic lesion other than primary lung cancer.

Survival Analyses

The 5-year survival rates were 84.6% for the overall cohort, 89.3% for the standard surgery, and 65.2% for the sublobar resection. The long-term survival after sublobar resection was significantly inferior to that after the standard surgery ($p = 0.0015$, Fig 1A). A multivariate analysis showed advanced age, sublobar resection, and nonadenocarcinoma to be independent significant unfavorable factors for the overall survival (Table 3). We further calculated the relative survival and performed an age-stratified analysis in each age group between the types of surgery. The 5-year relative survival rates of the younger patients were 90.9% (95% confidence interval [CI], 87.7% to 93.3%) for the standard surgery group and 64.0% (95% CI, 51.9% to 73.8%) for the sublobar resection group (Fig 1B). On the other hand, the difference between the types of surgery disappeared in the elderly patients (Fig 1C). The 5-year relative survival rates of the elderly patients were 74.3% (95% CI, 60.8% to 83.7%) for the standard surgery and 67.6% (95% CI, 51.7% to 79.3%) for the sublobar resection. To examine the survival effect between the types of surgery according to age group, we divided the patients into the following four groups: (I) younger patients who underwent standard lobectomy; (II) younger patients who underwent sublobar resection; (III) elderly patients who underwent lobectomy; and (IV) elderly patients who underwent sublobar resection. Thereafter, we calculated the hazard ratios for death of each patient group based on a multivariate Cox proportional model. Group I was used as a control group. As shown in Figure 2, while the hazard ratio of group II was 2.83 (95% CI, 1.84 to 4.35) as compared with the control group, the hazard ratio of group IV (2.64; 95% CI, 1.61 to 4.31) was similar to that of group III (2.97; 95%CI, 1.79 to 4.95).

Table 2. Reasons for Selecting Sublobar Resections

Reasons	Younger (<75 years) (n = 92) (%)	Elderly (≥75 years) (n = 54) (%)
Insufficient pulmonary function or chronic lung diseases	50 (54.3)	25 (46.3)
Insufficient cardiac function or cardiovascular diseases	22 (23.9)	20 (37.0)
Previous lung surgery or multiple lung cancer	14 (15.2)	7 (13.0)
Cancer history	9 (9.8)	3 (5.5)
Diabetes mellitus	4 (4.3)	6 (11.1)
Other	4 (4.3)	3 (5.5)

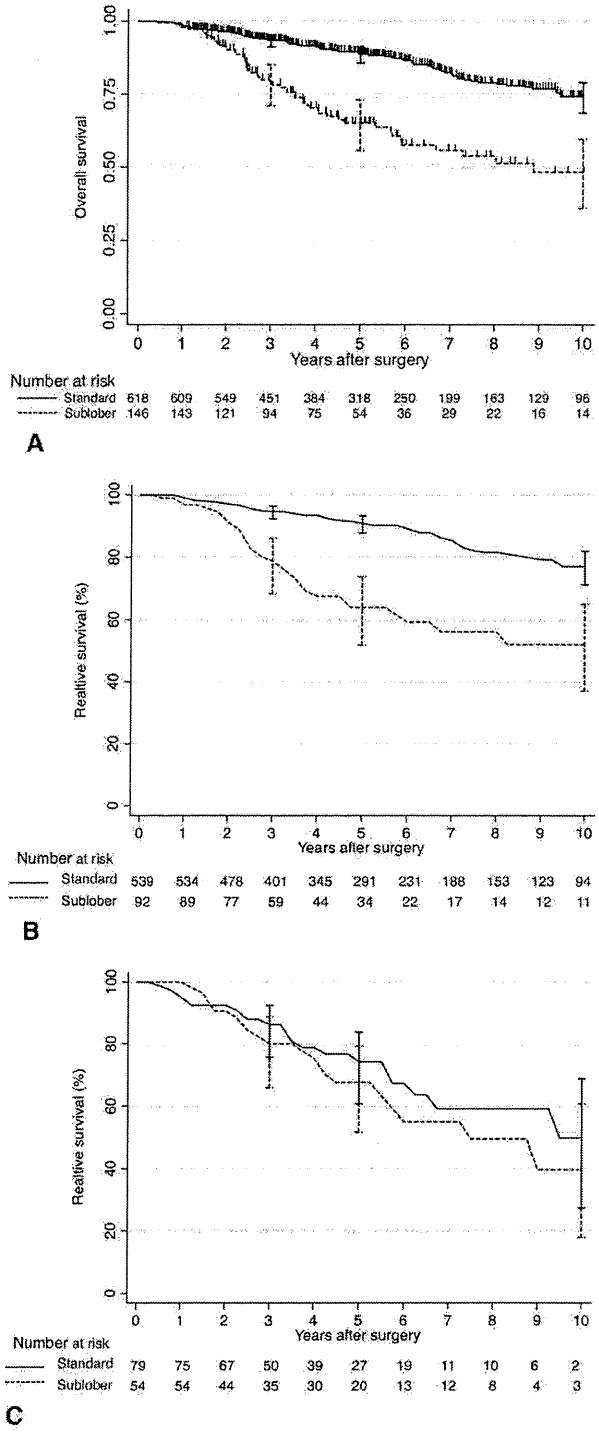

Fig 1. Postoperative survival curves according to the types of surgery (standard surgery or sublobar resection) with 95% confidence intervals at 3, 5, and 10 years after surgery. (A) The overall survival of the overall cohort (all ages); (B) the relative survival of the younger patients (<75 years); and (C) the relative survival of the elderly patients (≥75 years).

Table 3. Multivariate Analysis of Survival: Cox Proportional Hazard Model

Variable	HR	95% CI	*p* Value
Age	1.045	1.023–1.068	<0.0001
Operative procedure			
Standard surgery	ref		
Sublobar resection	1.835	1.261–2.670	0.0015
Histology			
Adenocarcinoma	ref		
Nonadenocarcinoma	1.739	1.160–2.604	0.0074
Gender			
Female	ref		
Male	1.324	0.786–2.231	0.2919
T stage			
T1a	ref		
T1b	1.018	0.716–1.447	0.9196
Smoking status			
Nonsmoker	ref		
Ex- or current smoker	1.178	0.687–2.020	0.8490

CI = confidence interval; HR = hazard ratio.

Postoperative Complications in the Elderly Patients

Thirty-five of the elderly patients (26.3%) experienced postoperative complications (Table 4). Life-threatening complications included two cases of acute myocardial infarction and one drug-induced anaphylactic shock. The occurrence of a life-threatening or a major complication was not associated with the types of surgery ($p = 0.3146$).

Recurrence of the Disease

Any recurrences of the disease during the follow-up period are summarized in Table 5. The percentages of distant metastasis ranged from 11.3% to 13.0% regardless the types of surgery or the patients' age. On the other hand, the local recurrence in the overall cohort apparently occurred more commonly in the patients who had

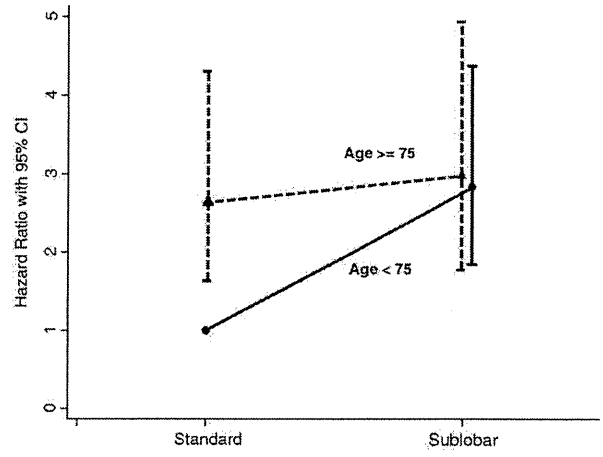

Fig 2. Comparison of the hazard ratio between standard surgery and sublobar resection in younger patients (solid line) and elderly patients (dashed line). (CI = confidence interval.)

Table 4. Postoperative Complications in the Elderly Patients

Complications	Standard (n = 79)	Sublobar (n = 54)
Life threatening (%)	1 (1.3)	2 (3.7)
Major (%)	4 (5.1)	5 (9.3)
Minor (%)	15 (19.0)	8 (14.8)

sublobar resection than in patients who had standard surgery (11.6% and 1.5%, respectively).

Comment

Removing the entire lobe, which contains the primary tumor, provides the highest probability for a complete resection of the disease including tumor cells spreading into adjacent pulmonary parenchyma and occult metastasis in the regional lymph nodes. However, surgeons often hesitate to recommend lobectomy for patients under comorbid conditions or with poor pulmonary function. Instead, sublobar resection such as wedge resection and segmentectomy are often offered to those patients in daily clinical practice to reduce surgical stress and to preserve more pulmonary function. This study revealed that sublobar resection provided an equivalent long-term outcome to that of lobectomy in the elderly patients.

The difference in the survival after lobectomy and sublobar resection has been debated even after one randomized trial demonstrated that sublobar resection for stage IA had a higher local recurrence rate and a shorter survival [10]. Nationwide retrospective studies in Japan and the US identified extent of surgical resection as a significant prognostic factor after curative resection for stage IA [11, 12]. These findings support the fact that lobectomy is the gold standard for stage IA lung cancer. On the other hand, studies focusing on elderly patients with stage IA revealed that anatomic segmentectomy was associated with reduced surgical risks and comparable oncologic efficacy [13]. Furthermore, according to the data from The National Cancer Registry in the United States, the statistical difference between survival curves of lobectomies and limited resections for stage I or II disappeared at 71 years of age [14]. In addition, the Japanese Joint Committee of Lung Cancer Registry also found no significant difference in the survival after lobectomy or sublobar resection for c-stage I of octogenarian patients [15].

Previously, several reports have demonstrated that sublobar resection was not inferior to standard lobectomy regarding the prognosis of patients with small-sized NSCLC [16, 17]. When comparing the outcomes of sublobar resection with that of lobectomy, it is important to mention the peripheral nodules, which are identified as a shadow containing ground-glass opacity by CT scanning. Most of such nodules are histologically diagnosed as early adenocarcinoma or minimally or noninvasive bronchioloalveolar carcinoma. The long-term result of this disease is excellent and the 5-year survival rate reaches to more than 96% even after sublobar resection [18, 19]; in contrast, the 5-year survival of NSCLC at stage IA is reported to be 83.9% [20]. Therefore, in order to elucidate the outcomes after sublobar resection in compromised patients, it is necessary to exclude the patients who underwent wedge resection or segmentectomy for this distinct subset of early-stage lung cancer. Otherwise, the outcome of the sublobar resection group might be spuriously superior to that of patients who underwent the same treatment due to their impaired medical condition. We have established institutional criteria based on the CT findings to indicate a sublobar resection with a radical intent for peripheral noninvasive carcinoma [5]. These criteria defined the patients who underwent sublobar resection due to the patients' medical and (or) physiologic condition. Therefore, the results of sublobar resection shown in this study were solely derived from patients who demonstrated medically impaired conditions.

The long-term results of p-stage IA based on the new staging system in the present study, 89.0% after the standard surgery and 65.3% after sublobar resection without any operative mortality, were satisfactory. As previously reported [12], age proved to be an independent predictor of survival in patients with stage IA. The patients were stratified by age group to eliminate an effect of the different distribution of the patients' age between the standard surgery and the sublobar resection. Furthermore, to consider the effect of background mortality, the relative survival was calculated and the prognosis was compared adequately between the types of surgery. One of the important findings in this study is that sublobar resection was a strong independent predictor for shortened survival in the overall cohort, but the types of surgery, standard or sublobar resection, did not affect the survival in the elderly patients. Multivariate analysis revealed that the unfavorable effect of sublobar resection on survival was apparent in the younger patients whereas the hazard ratio of sublobar resection was similar to that of standard lobectomy among elderly patients.

Following the equivalent survival in the elderly, postoperative complications were also studied. The occurrence of complications after sublobar resection did not increase in comparison with that after standard lobectomy even though the patients in the sublobar group were compromised. The reduced surgical intervention using lesser extent of pulmonary resection may contribute to this favorable result. The types of recurrence were

Table 5. Recurrence of the Disease From the Overall Cohort and Each Age Group

	Younger (<75 years)		Elderly (≤75 years)	
Type of recurrence	Standard (n = 539)	Sublobar (n = 92)	Standard (n = 79)	Sublobar (n = 54)
Locoregional (%)	8 (1.5)	11 (12.0)	1 (1.3)	6 (11.1)
Distant (%)	61 (11.3)	12 (13.0)	10 (12.7)	7 (13.0)