Table 3. Characteristics of Patients With Clinical T1b Tumors That Met the Node-Negative Criteria

Variables[a]	Solid Tumor Size <0.8 cm or SUVmax <1.5 (n = 106)
Age, y	67.5 (33–89)
Male sex	48 (45.3)
Whole tumor size, cm	2.4 (2.1–3.0)
Solid tumor size, cm	0.6 (0–2.5)
SUVmax	1.0 (0–4.1)
Adenocarcinoma in situ	19 (17.9)
Procedure	
Lobectomy	67 (63.2)
Sublobar resection	39 (36.8)
Segmentectomy	22 (20.8)
Wedge resection	17 (16.0)
Lymphatic invasion	2 (1.9)
Vascular invasion	2 (1.9)
Pleural invasion	2 (1.9)
Lymph node metastasis	0 (0)
Recurrence	0 (0)

[a] Categoric data are shown as number (%) and continuous data as median (range).

SUVmax = maximum standardized uptake value.

sublobar resection if there are sufficient surgical margins. Cox proportional hazards model in this subpopulation also supported the use of sublobar resection. To achieve complete resection with adequate margins, we recommend segmentectomy, but not wedge resection, for T1b tumors meeting these N0 criteria, because providing an adequate margin for T1b tumors by wedge resection is difficult. The extent of resection should be chosen according to tumor size and location, and procedures that can lead to local recurrence must be avoided.

A benefit of sublobar resection is preservation of lung function [3, 14, 15]. In addition, sublobar resection provides outcomes that are equivalent to those of lobectomy for patients selected on the basis of HRCT and FDG-PET/CT findings; therefore, this can be a suitable procedure for these patients. However, 47 of 293 patients who did not meet the N0 criteria and could have possibly had lymph node metastasis underwent sublobar resection. The RFS rate for patients who underwent sublobar resection appeared to be worse than that for patients who underwent lobectomy, although the results were not significantly different ($p = 0.058$). Among 47 patients in the sublobar resection group, 24 (51%) underwent wedge resection. Therefore, patients who do not meet the N0 criteria (solid tumor size >0.8 cm and SUVmax >1.5) should be treated with segmentectomy or lobectomy with systematic hilar and mediastinal lymph node dissection, not wedge resection, because they may have LN metastasis. If segmentectomy is applied to patients who do not meet the N0 criteria, intraoperative lymph node examinations using frozen sections are mandatory. When lymph node metastasis is detected intraoperatively, the procedure should be converted to a lobectomy.

Table 4. Multivariate Cox Analysis for Recurrence-Free Survival (All Patients)

Variables	HR (95% CI)	*p* Value
Age	1.02 (0.99–1.04)	0.24
Sex (male)	1.06 (0.67–1.68)	0.80
Solid tumor size (cm)	2.04 (1.47–2.81)	<0.001
SUVmax	1.15 (1.07–1.24)	<0.001
Procedure (lobectomy)	0.64 (0.35–1.18)	0.15

CI = confidence interval; HR = hazard ratio; SUVmax = maximum standardized uptake value.

Table 5. Multivariate Cox Analysis for Recurrence-Free Survival (Clinical T1b Patients)

Variables	HR (95% CI)	*p* Value
Age	1.02 (0.98–1.06)	0.40
Sex (male)	1.43 (0.75–2.73)	0.28
Solid tumor size (cm)	1.44 (0.88–2.36)	0.14
SUVmax	1.25 (1.12–1.39)	<0.001
Procedure (lobectomy)	0.83 (0.29–2.34)	0.72

CI = confidence interval; HR = hazard ratio; SUVmax = maximum standardized uptake value.

A strength of this study was that HRCT and FDG-PET/CT were performed for all patients and could be used to analyze the details of tumor morphology and glucose metabolism. In addition, SUVmax on FDG-PET/CT is a known prognostic factor for NSCLC, particularly adenocarcinoma [11, 13, 16–22]. Furthermore, we used an anthropomorphic body phantom to minimize interinstitutional SUV variability, which is a major limitation of multicenter PET studies.

Although this was a retrospective study, our updated database included a large number of patients with moderate follow-up periods. This allowed us to validate our N0 criteria and conclude that sublobar resection was useful for patients who met these criteria. Longer follow-up periods will be needed to ensure that these results are reliable.

This study had several limitations. Because this was a retrospective study, patients who underwent sublobar resection were possibly highly selected. In addition, preoperatively verifying the histologic origin of a tumor, particularly small tumors, is sometimes difficult. The lack of data on comorbid conditions and lung function also limited the definitive conclusion that sublobar resection is not less effective than lobectomy for clinical stage IA lung adenocarcinoma. A prospective study to assess the prognostic significance of sublobar resection for patients who meet our proposed N0 criteria is warranted.

In conclusion, we demonstrated that sublobar resection was feasible for patients with clinical stage IA lung adenocarcinomas that met our proposed N0 criteria of solid tumor size of less than 0.8 cm on HRCT or a SUVmax of less than 1.5 on FDG-PET/CT, with a survival rate equivalent to that associated with standard lobectomy. Even a T1b tumor, which is generally unsuitable for

intentional sublobar resection, can be a candidate for sublobar resection if it meets these N0 criteria and has adequate surgical margins.

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Featured Article

Segmentectomy versus lobectomy for clinical stage IA lung adenocarcinoma

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Background: Despite the increasing prevalence of the early discovery of small-sized non-small cell lung cancers (NSCLCs), particularly adenocarcinoma, sublobar resection has not yet gained acceptance for patients who can tolerate lobectomy.

Methods: We compared the outcomes of segmentectomy (n=155) and lobectomy (n=479) in 634 consecutive patients with clinical stage IA lung adenocarcinoma and in propensity score-matched pairs. Those who had undergone wedge resection were excluded.

Results: The 30-day postoperative mortality rate in this population was zero. Patients with large or right-sided tumors, high maximum standardized uptake value (SUVmax), pathologically invasive tumors (with lymphatic, vascular, or pleural invasion), and lymph node metastasis underwent lobectomy significantly more often. Three-year recurrence-free survival (RFS) was significantly higher after segmentectomy compared to lobectomy (92.7% *vs.* 86.9%, P=0.0394), whereas three-year overall survival (OS) did not significantly differ (95.7% *vs.* 94.1%, P=0.162). Multivariate analyses of RFS and OS revealed age and SUVmax as significant independent prognostic factors, whereas gender, tumor size and procedure (segmentectomy *vs.* lobectomy) were not. In 100 propensity score-matched pairs with variables adjusted for age, gender, tumor size, SUVmax, tumor location, the three-year RFS (90.2% *vs.* 91.5%) and OS (94.8% *vs.* 93.3%) after segmentectomy and lobectomy respectively were comparable.

Conclusions: Segmentectomy with reference to SUVmax should be considered as an alternative for clinical stage IA adenocarcinoma, even for low-risk patients.

Keywords: Adenocarcinoma; segmentectomy; sublobar resection; lung cancer; lobectomy

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Introduction

Sublobar resection for intentionally treating patients with small non-small cell lung cancer (NSCLC) who are able to withstand lobectomy has remained highly controversial, although lobectomy is considered a standard procedure even for sub-centimeter lung cancers. The Lung Cancer Study Group (LCSG) revealed a three-fold increase in local recurrence rates and poorer survival in patients who had undergone sublobar resection rather than lobectomy in a singular randomized phase III study published in 1995 (1). The dogma that lobectomy is the standard of care for stage I NSCLC has been upheld until recently. However, several current investigations have found equivalent outcomes of sublobar resection and lobectomy when NSCLC are ≤2 cm (2-7).

Sublobar resection consists of segmentectomy and wedge resection, which are quite different from each other as

curative surgery for lung cancer, since segmentectomy is more likely to provide sufficient margins and allows access to subsegmental and hilar lymph nodes. The present study retrospectively compared the outcomes of segmentectomy, not wedge resection and lobectomy among patients with clinical stage IA lung adenocarcinoma, and adjusted for clinical factors to minimize selection bias of patients. This analysis is an extended and updated version of our previous investigation (8).

Patients and methods

We analyzed data from 634 patients who had undergone lobectomy and segmentectomy for clinical T1N0M0 stage IA lung adenocarcinoma since October 2005. All patients were assessed using high-resolution computed tomography (HRCT) and F-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). Patients with incompletely resected (R1 or R2) or multiple tumors were excluded from the prospectively maintained database that was analyzed herein. All patients were staged according to the TNM Classification of Malignant Tumors, 7th edition (9). Platinum-based chemotherapy was administered to patients with pathological lymph node metastasis after surgery. The institutional review boards of the participating institutions approved the study and the requirement for informed consent from individual patients was waived because the study was a retrospective review of a database. Chest images were acquired by multi-detector HRCT independently of subsequent FDG-PET/CT examinations. Tumor sizes and maximum standardized uptake values (SUVmax) were determined by radiologists at each institution. Because of the heterogeneity of PET techniques and performance, we corrected inter-institutional errors in SUVmax resulting from PET/CT scanners of variable quality based on outcomes of a study using an anthropomorphic body phantom (NEMA NU2-2001, Data Spectrum Corp, Hillsborough, NC, USA) that conformed to National Electrical Manufacturers Association standards (10). A calibration factor was analyzed by dividing the actual SUV by the gauged mean SUV in the phantom background to decrease inter-institutional SUV inconsistencies. Postoperative follow-up of all patients from the day of surgery included physical examinations and chest X-rays every three months, as well as chest and abdominal CT and brain MRI assessments every six months for the first two years. Thereafter, the patients were assessed by physical examinations and chest X-rays every six months, and annual CT and MRI imaging.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences software version 10.5 (SPSS Inc., Chicago, IL, USA). Continuous variables were compared using *t*-tests and Mann-Whitney *U* tests in all cohorts and Wilcoxon tests for propensity-matched pairs. Frequencies of categorical variables were compared using the χ^2 test and propensity-matched pairs were analyzed using McNemar tests. Propensity score matching was applied to balance the assignments of the included patients and to correct for the operative procedures (lobectomy or segmentectomy) that confounded survival calculations. The variables of age, sex, tumor size, SUVmax, side and lobe were multiplied by a coefficient that was calculated from logistic regression analysis, and the sum of these values was taken as the propensity score for each patient. Lobectomy and segmentectomy pairs with equivalent propensity scores were selected by a 1-to-1 match.

We defined recurrence-free survival (RFS) as the time from the day of surgery until the first event (relapse or death from any cause) or last follow-up, and overall survival (OS) as the time from the day of surgery until death from any cause or the last follow-up. The durations of RFS and OS were analyzed using the Kaplan-Meier method, and differences in RFS and OS were assessed using the log-rank test. Both RFS and OS were assessed by multivariate analysis using the Cox proportional hazards model.

Results

Of the 634 patients analyzed in this study, 479 and 155 underwent lobectomy and segmentectomy, respectively (*Table 1*). Patients with large tumors, right-sided tumors, pathologically invasive tumors, (presence of lymphatic, vascular, or pleural invasion), high SUVmax, and lymph node involvement were significantly more often treated by lobectomy. However, age and gender did not differ significantly between the two procedures. *Table 2* shows the segments that were removed during segmentectomy.

None of the patients died within 30 days of surgery, and tumors recurred in 54 patients at a median postoperative follow-up period of 34.2 months. Twenty recurrences were local only and 34 were distant (with or without local recurrence). Local recurrence occurred in 17 patients after

Table 1 Patient characteristics

Variables	Lobectomy (n=479)	Segmentectomy (n=155)	P value
Age	66 [30-89]	66 [31-89]	0.37
Gender			
Male	223 (46.6%)	74 (48.1%)	0.78
Tumor size (cm)	2.2 (0.7-3.0)	1.5 (0.6-3.0)	<0.001
SUVmax†	2.1 (0-16.9)	1.1 (0-9.8)	<0.001
Side			
Right	325 (67.8%)	81 (52.3%)	<0.001
Lobe			<0.001
Upper	254 (53.0%)	82 (52.9%)	
Middle	48 (10.0%)	0 (0%)	
Lower	177 (37.0%)	73 (47.1%)	
Lymphatic invasion	97 (20.3%)	10 (6.5%)	<0.001
Vascular invasion	111 (23.3%)	10 (6.5%)	<0.001
Pleural invasion	66 (13.9%)	8 (5.2%)	0.0024
Lymph node metastasis	50 (10.6%)	3 (1.9%)	<0.001

†, maximum standardized uptake value.

Table 2 Details of segmentectomy (n=155)

Site	Number
Right (n=81)	
S1	11
S1+2	1
S2	13
S3	7
S6	31
S7	3
S8	8
S9	1
S10	1
S7+8	1
S8+9	2
S9+10	1
S7+8+9+10	1
Left (n=74)	
S1+2	17
S3	9
S1+2+3	10
S1+2+3c	1
S4	5
S5	1
S4+5	7
S6	15
S8	2
S9	5
S10	1
S8+9+10	1

lobectomy (hilar lymph node, n=1; mediastinal lymph node, n=11; pleura, n=2; hilar and mediastinal lymph nodes, n=1; bronchial stump and mediastinal lymph node, n=1; mediastinal lymph node and pleura, n=1) and in three patients after segmentectomy (bronchial stump, n=1; pleura, n=1; residual lung and mediastinal lymph node, n=1).

The 3-year OS rates between patients who underwent lobectomy and segmentectomy were similar (94.1% *vs.* 95.7%, P=0.162), whereas three-year RFS rates significantly differed (86.9% *vs.* 92.7%, P=0.0394; *Figure 1*). *Table 3* shows that the multivariate analyses of RFS and OS selected age and SUVmax as significant independent prognostic factors, but not sex, tumor size, or procedure (lobectomy *vs.* segmentectomy).

Propensity score-matching based on clinical variables of age, gender, tumor size, SUVmax, side and lobe, allowed good matches of 100 lobectomy and segmentectomy pairs in terms of clinical and consequently pathological factors, except for more advanced age and higher SUVmax in the segmentectomy group (*Table 4*). Patients who underwent middle lobectomy were excluded from matching for a fair comparison, since tumors located in a middle lobe were never treated by segmentectomy. *Figure 1* shows that the three-year RFS and OS did not significantly differ between propensity score-matched patients after lobectomy or segmentectomy (91.5% *vs.* 90.2% and 93.3% *vs.* 94.8%, respectively).

Discussion

The RFS and OS curves of patients with clinical stage IA lung adenocarcinoma seemed better after segmentectomy than lobectomy, although the clinical and pathological backgrounds significantly differed and would obviously affect their survival (11-16). Multivariate analyses of the clinical background for RFS and OS demonstrated that procedure (lobectomy *vs.* segmentectomy) was not a significant prognostic factor. The clinical features or

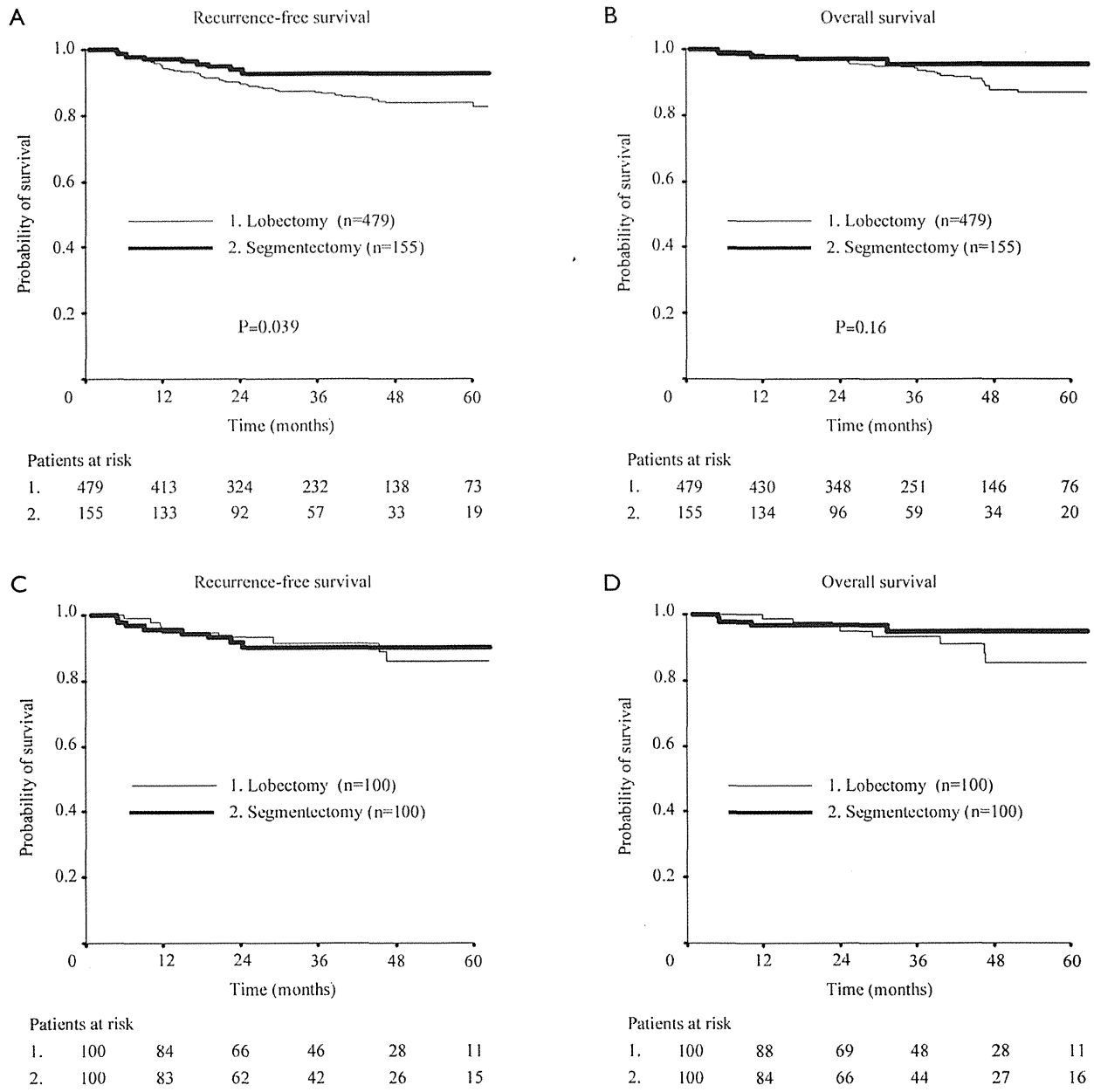

Figure 1 Recurrence-free (RFS) and overall survival (OS) curves of patients after lobectomy and segmentectomy. Three-year RFS (A) and OS (B) after lobectomy and segmentectomy were 86.9% *vs.* 92.7% (P=0.0394) and 94.1% *vs.* 95.7% (P=0.162), respectively, in all cohorts. Three-year RFS (C) and OS (D) in propensity score-matched patients after lobectomy and segmentectomy were 91.5% *vs.* 90.2% and 93.3% *vs.* 94.8%, respectively.

pathological factors of lymphatic, vascular or pleural invasion, or lymph node metastasis were similar in propensity score-matching analyses that matched for potentially confounding variables of age, sex, tumor size, SUVmax, tumor location to minimize selection bias. Only age and SUVmax significantly differed. The three-year RFS and OS rates after segmentectomy and lobectomy group were similar in the matched model, although the former

Table 3 Multivariate analyses for RFS and OS

Variables	HR (95% CI)	P value
Multivariate analysis for RFS[†]		
Age	1.04 (1.01-1.07)	0.011
Gender		
Male *vs.* female	1.20 (0.74-1.93)	0.46
Tumor size (cm)	1.36 (0.86-2.14)	0.19
SUVmax[‡]	1.17 (1.09-1.25)	<0.001
Procedure		
Lobectomy *vs.* segmentectomy	0.72 (0.34-1.52)	0.39
Multivariate analysis for OS[#]		
Age	1.05 (1.01-1.09)	0.0082
Gender		
Male *vs.* female	1.10 (0.49-1.70)	0.78
Tumor size (cm)	1.23 (0.67-2.26)	0.50
SUVmax[‡]	1.13 (1.04-1.24)	0.0068
Procedure		
Lobectomy *vs.* segmentectomy	0.68 (0.25-1.82)	0.44

RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval. [†], recurrence-free survival; [‡], maximum standardized uptake value; [#], overall survival.

Table 4 Propensity score-matched comparison of clinical and pathologic factors between patients who underwent lobectomy and segmentectomy

Variables	Lobectomy (n=100)	Segmentectomy (n=100)	P value
Clinical factors			
Age	63 [33-82]	66 [32-89]	0.030
Gender			
Male	46 (46%)	50 (50%)	0.67
Tumor size (cm)	1.6 (0.7-3.0)	1.6 (0.6-3.0)	0.28
SUVmax[†]	1.2 (0-8.7)	1.2 (0-9.8)	0.047
Side			0.27
Right	62 (62%)	53 (53%)	
Lobe			0.10
Upper	62 (62%)	50 (50%)	
Lower	38 (38%)	50 (50%)	
Pathologic factors			
Lymphatic invasion	11 (11%)	7 (7%)	0.45
Vascular invasion	9 (9%)	9 (9%)	1.0
Pleural invasion	10 (10%)	7 (7%)	0.61
Lymph node metastasis	7 (7%)	3 (3%)	0.34

[†], maximum standardized uptake value.

were significantly older and had a higher SUVmax. These data suggest that segmentectomy could be an alternative strategy for treating clinical stage IA lung adenocarcinoma when HRCT and FDG-PET/CT findings are taken into consideration.

This investigation has several limitations and the results should be interpreted with care. Information in the database analyzed herein included surgical procedures; however, further details such as indications for segmentectomy—that is, whether or not patients who were treated with segmentectomy could have tolerated lobectomy—are difficult to obtain. In addition, patients who underwent segmentectomy tended to have less invasive, smaller tumors, with small tumor size or low SUVmax, and thus a lower frequency of pathologically invasive factors such as lymphatic, vascular, pleural or nodal involvement. Therefore, we used propensity score-matched analysis to adjust the patients' backgrounds as much as possible. However, we could not compare the surgical outcomes of patients with a relatively low SUVmax, implying that patients with a high SUVmax require close scrutiny. The database also did not include information about lung function. The key advantage of segmentectomy is the preservation of lung function, and several studies have shown that segmentectomy has functional advantages over lobectomy (5,17,18).

The target tumors of most previous studies that compared the outcomes of segmentectomy and lobectomy were T1 N0 M0 NSCLC of ≤2 cm (4-6). However, the present study included patients with clinical T1b tumors of 2 to 3 cm. Patients with T1b lung adenocarcinomas with a sufficient surgical margin could be candidates for sublobar resection if selected based on HRCT and FDG-PET/CT findings (12).

The ongoing, multicenter phase III clinical trials of propriety of radical segmentectomy in the United States (CALGB-140503) and Japan (JCOG0802/WJOG4607L) should be carefully monitored. The primary end-point of the Japanese study is OS (disease-free survival in the US study), and wedge resection is not permitted as a sublobar resection, as it differs from radical segmentectomy. The Japanese study (19) aims to compare the surgical outcomes

of lobectomy and segmentectomy for T1 N0 M0 NSCLC measuring ≤2 cm, excluding radiologically less-invasive tumors such as ground-glass opacity (GGO)-dominant tumors on HRCT (20), and thus can show the true colors of segmentectomy compared with lobectomy. Segmentectomy is more procedurally demanding than either lobectomy or wedge resection, and thus incorrect outcomes of these clinical trials due to technical errors, such as recurrence at resection lines or excessive loss of lung function, might be a concern. Surgeons must carefully avoid local failure at the margin and fully expand adjacent segments to maximize postoperative lung function.

Current understanding of radical segmentectomy can be summarized as follows. Firstly, the indication for segmentectomy should be limited to T1 tumors ≤3 cm in diameter, and HRCT and PET-CT findings must be taken into consideration, particularly for T1b tumors (21-23). Whenever nodal involvement or an insufficient margin is confirmed intraoperatively, segmentectomy should be converted to lobectomy with complete nodal dissection. Secondly, radical (intentional) and compromising indications for segmentectomy must be independently discussed. The former is for low-risk patients who can tolerate lobectomy. Thirdly, segmentectomy is more valuable than wedge resection from an oncological perspective because it allows nodal dissection at the hilum. Thus, the decision of the most suitable procedure, such as whether or not to intraoperatively convert to lobectomy, should consider precise staging and the lower rate of local recurrence resulting from sufficient surgical margins. Therefore, segmentectomy must be clearly separated from wedge resection amongst the categories of sublobar resection for lung cancer. Surgeons must become adept and master segmentectomy as a keynote procedure because small lung cancers are being detected with increasing frequency.

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Comparison of chemotherapeutic efficacy between LCNEC diagnosed using large specimens and possible LCNEC diagnosed using small biopsy specimens

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ORIGINAL ARTICLE

Comparison of chemotherapeutic efficacy between LCNEC diagnosed using large specimens and possible LCNEC diagnosed using small biopsy specimens

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Abstract
Background It is often difficult to diagnose large cell neuroendocrine carcinomas (LCNEC) of the lung using small biopsy specimens. Some recent studies attempted to diagnose LCNEC using biopsy specimens; in 2011, the International Association for the Study of Lung Cancer pathological panels suggested possible LCNEC as a diagnosis for LCNEC by using biopsy specimens. Here, we compared the chemotherapeutic efficacy in possible LCNEC and LCNEC diagnosed using surgically resected specimens.
Methods We retrospectively reviewed patients who received platinum-based chemotherapy as first-line chemotherapy at our institution during September 2002–September 2011. Further, we compared the clinical characteristics, chemotherapeutic responses, and survival outcomes of patients diagnosed as having "LCNEC definite" with those diagnosed as having "possible LCNEC."
Results We selected 34 patients of whom 10 were diagnosed with LCNEC using surgically resected specimens and 24 patients with possible LCNEC were diagnosed using small biopsy specimens. In both groups, almost all patients were men and were smokers. Small-cell carcinoma-based chemotherapy, such as platinum plus irinotecan or platinum plus etoposide, was used for treating 60 % LCNEC patients (6/10) and 67 % possible LCNEC patients. In the LCNEC and possible LCNEC groups, respectively, the response rate was 70 and 54 % ($p = 0.39$), median progression-free survival was 2.9 and 4.4 months ($p = 0.20$), and median survival time was 12.8 and 9.1 months ($p = 0.50$).
Conclusion No statistically significant differences were found in chemotherapeutic responses and survival outcomes between the 2 groups, which suggests that chemotherapeutic efficacy is similar in both possible LCNEC and LCNEC.

Keywords LCNEC · Possible LCNEC · Small cell carcinoma · Chemotherapy · Biopsy

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Introduction

In the 2004 edition of the World Health Organization (WHO) classification, large cell neuroendocrine carcinoma (LCNEC) of the lung was defined using detailed criteria for each subtype of neuroendocrine tumor; LCNEC was subcategorized as a variant of large cell carcinoma. The histological findings of LCNEC are large tumor cells with a low nuclear/cytoplasm ratio, prominent nucleoli, a high

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mitotic rate (11 or more mitotic figures in 10 high-power fields), a high degree of necrosis, and neuroendocrine (NE) morphologic features, such as rosette formation, organoid nesting, and palisading. Immunohistochemical positive staining for at least 1 NE marker, such as neural cell adhesion molecule (NCAM), chromogranin A, and synaptophysin, is also required [1].

LCNEC is a rare tumor accounting for approximately 3 % of all resected pulmonary malignancies [2–4]. Most previous reports have found that LCNEC predicted poorer survival than expected for stage-matched non-small-cell lung carcinoma (NSCLC) [2–4]. The malignant behavior and poor prognosis of LCNEC have been reported to be similar to those of small-cell lung carcinoma (SCLC) [5, 6]. However, these reports were limited to surgically resected specimens, because it is difficult to fully meet the histological criteria required to diagnose LCNEC using small biopsy specimens. One of the serious problems with LCNEC is that there are few studies evaluating the clinical features and prognosis of advanced cases, since diagnosis of advanced LCNEC using a small specimen is often difficult. There is no established therapeutic strategy for LCNEC, particularly for advanced cases.

Recently, Igawa et al. [7] attempted to diagnose advanced LCNEC using biopsy specimens, and reported that the pathological findings of LCNEC on biopsy specimens were defined NSCLC with some NE morphology and 1 or more positive NE markers with a high Ki-67/MIB 1 labeling index. Shimada et al. [8] also reported similar results. In 2011, Travis and colleagues suggested use of the term "possible LCNEC" for NSCLC with NE morphology and positive NE markers (NCAM, chromogranin A, and/or synaptophysin), excluding definite adenocarcinoma and squamous cell carcinoma, in a small biopsy specimen [9]. To evaluate the diagnosis of possible LCNEC, we compared the efficacy of chemotherapy in LCNEC and possible LCNEC in this study.

Patients and methods

Patients

From September 2002 to September 2011, we selected patients consecutively whose pathological diagnoses were LCNEC or possible LCNEC who received platinum-based chemotherapy as first-line chemotherapy from patient records at Shizuoka Cancer Center. We excluded patients who received concurrent chemo-radiotherapy. LCNEC and possible LCNEC were diagnosed using either primary or metastatic lesions. The sampling method was not defined, i.e., whether it was by biopsy or surgery. LCNEC was diagnosed according to the 2004 WHO criteria, using samples obtained by surgically resection. The diagnosis of possible LCNEC was made when LCNEC was highly suspected, but it was difficult to fulfill the conventional WHO criteria. All cases had confirmed positivity of 1 or more immunohistochemical NE markers (NCAM, chromogranin A, and synaptophysin) and showed a high MIB 1 labeling index (more than 40 %).

Evaluation

Chemotherapeutic response was accessed according to the Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST guideline (version 1.1) [10]. To define disease progression or relapse, patients were evaluated by physical examination, chest radiography, and computed tomography (CT) of the chest and abdomen. In some patients, we used positron emission tomography (PET)–CT, magnetic resonance imaging (MRI), or bone scintigraphy to detect the extent of disease progression. Their clinical disease staging was reassessed according to the latest Union for International Cancer Control (UICC) staging criteria (7th edition) [11].

Progression-free survival (PFS) was scored as an event of documented disease recurrence or death measured from the start of first-line chemotherapy to the date of an event or the last follow-up. Overall survival (OS) was measured from the start of first-line chemotherapy to the date of death or the last follow-up.

Statistical analysis

All categorical variables and objective response rates were analyzed using the chi-squared test or Fisher's exact test, as appropriate. Distributions of PFS and OS were estimated using the Kaplan–Meier method, and the LCNEC and possible LCNEC groups were compared using the log-rank test. All p values were 2 sided, and values <0.05 were considered statistically significant. All analyses were performed using JMP 9 software (SAS Institute, Cary, NC, USA). This study was approved by the institutional review board.

Results

A total of 34 patients were eligible for this retrospective study, including 10 LCNEC patients diagnosed using surgically resected specimens. The resection sites for diagnosis of LCNEC were the lung ($n = 6$), brain metastasis ($n = 3$), and bone metastasis ($n = 1$). All 24 possible LCNEC patients were diagnosed using small biopsy specimens, and the biopsy sites were transbronchial biopsy ($n = 18$), CT-guided needle biopsy ($n = 4$), surgical

Table 1 Patient characteristics

Characteristic	LCNEC	Possible LCNEC	*p* value
Number of patients	10	24	–
Age			
Median (range)	69 (57–83)	67 (57–78)	0.29
Gender			
Male	10	20	–
Female	0	4	
Smoking status			
Ever	10	23	–
Never	0	1	
ECOG-PS			
0	1	4	0.17
1	9	16	
2	0	4	
Stage			
IIIA	0	1	<0.01
IIIB	0	1	
IV	4	22	
Recurrence after surgery	6[a]	0	

LCNEC large cell neuroendocrine carcinoma of the lung, *ECOG-PS* Eastern Cooperative Oncology Group performance status

[a] pStage IB (4), pStage IIIA (2)

pericardium biopsy ($n = 1$), and transanal colon biopsy ($n = 1$). Positive rates in immunohistochemical staining for NE markers were as follows: NCAM was 10 (100 %) in LCNEC and 22 (92 %) in possible LCNEC, chromogranin A was 5 (50 %) in LCNEC and 12 (50 %) in possible LCNEC, and synaptophysin was 7 (70 %) in LCNEC and 16 (67 %) in possible LCNEC.

Patient characteristics are shown in Table 1. Age was similar in the LCNEC and possible LCNEC groups ($p = 0.29$). All LCNEC patients were male and ever smokers. Among the 24 possible LCNEC patients, 83.3 % were male and only 1 patient was a never smoker. Four possible LCNEC patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2, but no statistically significant difference in PS was found between the 2 groups ($p = 0.17$). There was a difference in stage between the 2 groups ($p < 0.05$). Among the 10 LCNEC patients, 4 patients had distant metastasis (stage IV) and 6 patients had pulmonary recurrence after surgery. All possible LCNEC patients had stage III or IV disease.

The chemotherapy regimens used are shown in Table 2. Most patients were treated with SCLC-based regimens such as platinum plus irinotecan or platinum plus etoposide. Four LCNEC patients and 11 possible LCNEC patients were treated with cisplatin plus irinotecan. Two LCNEC patients and 5 possible LCNEC patients were treated with platinum plus etoposide.

Table 2 Chemotherapy regimens

	LCNEC ($n = 10$)	Possible LCNEC ($n = 24$)
Cisplatin plus irinotecan	4	11
Cisplatin plus etoposide	0	1
Carboplatin plus etoposide	2	4
Carboplatin plus paclitaxel	4	4
Others	0	4[a]

LCNEC large cell neuroendocrine carcinoma of the lung

[a] Cisplatin plus paclitaxel (1), cisplatin plus docetaxel (1), cisplatin plus vinorelbine (1), carboplatin plus S-1 (1)

Table 3 Clinical response to first-line chemotherapy

Response	LCNEC	Possible LCNEC	*p* value
CR	1	1	
PR	6	12	
SD	1	7	
PD	2	3	
NE	0	1	
Response rate (%)	70	54	0.39
95 % CI	40–90	35–72	

LCNEC large cell neuroendocrine carcinoma of the lung, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *CI* confidence interval

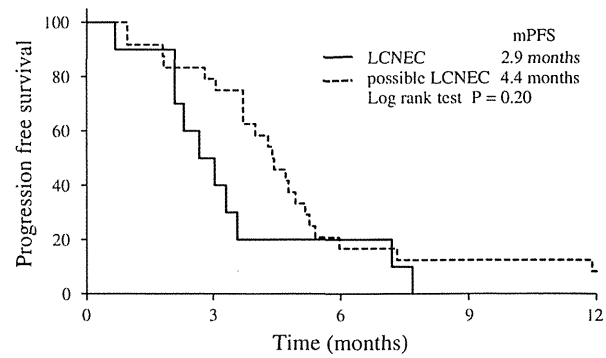

Fig. 1 Kaplan–Meier plot of progression-free survival (PFS) of patients with large cell neuroendocrine carcinomas (LCNEC) and possible LCNEC. The median PFS was 2.9 months in patients with LCNEC and 4.4 months in patients with possible LCNEC ($p = 0.20$)

The response rate was 70 % in LCNEC patients and 54 % in possible LCNEC patients (Table 3); and no statistically significant difference was found ($p = 0.39$).

The Kaplan–Meier curve for PFS is shown in Fig. 1. The median PFS was 2.9 months in the LCNEC group and 4.4 months in the possible LCNEC group ($p = 0.20$). The Kaplan–Meier curve for OS is shown in Fig. 2. The median

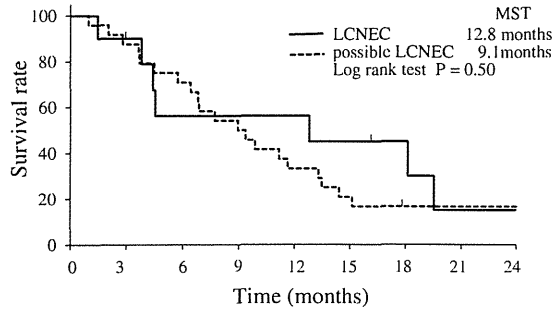

Fig. 2 Kaplan–Meier plot of overall survival of patients with large cell neuroendocrine carcinomas (LCNEC) and possible LCNEC. The median survival time (MST) was 12.8 months in patients with LCNEC and 9.1 months in patients with possible LCNEC ($p = 0.50$)

survival time (MST) was 12.8 months in the LCNEC group and 9.1 months in the possible LCNEC group ($p = 0.50$). In the present study, the median follow-up duration was 23.2 months.

Nine LCNEC patients and 15 possible LCNEC patients received second-line chemotherapy. Six LCNEC patients and 6 possible LCNEC patients were treated with amrubicin. Only 1 LCNEC patient who was treated with amrubicin showed a partial response.

Discussion

To the best of our knowledge, the present study is the first report comparing the efficacy of chemotherapy for LCNEC in patients diagnosed with LCNEC with that in patients diagnosed with possible LCNEC. In the present study, in the possible LCNEC group, the response rate was 54 % and the MST was 9.1 months. No statistically significant differences in the response rate and OS were found between the 2 groups.

Igawa et al. [7] evaluated 14 advanced possible LCNEC cases and showed that the response rate was 50 % and the MST was 10 months. In addition, Shimada et al. [8] analyzed 13 patients regarded as possible LCNEC with high-grade neuroendocrine carcinoma of the lung and reported that the response rate to first-line chemotherapy was 61 % and the MST was 12 months. These results were comparable to those of extensive disease (ED)-SCLC [7, 8] and to those in the possible LCNEC group in the present study. Resected LCNEC has been reported to be similar to SCLC in clinicopathological features and prognosis [5, 6].

Mazieres et al. [12] reported that 13 cases (72 %) of resected LCNEC relapsed with distant metastases, and 10 of these relapsed within 6 months. The 13 relapsed LCNEC cases were treated with platinum plus etoposide, and the response rate was 20 %. Other authors reported that the response rate of LCNEC was 50–59 % and the MST was 8–10.3 months, with most recurrences occurring after surgery [13, 14]. For LCNEC cases treated with cisplatin-based chemotherapy, the response rate was comparable to that of SCLC. Rossi et al. [15] reported that in 12 patients treated with platinum plus etoposide, the response rate was 50 % and the MST was 51 months, although 3 cases received radiotherapy in addition to chemotherapy. In previous studies, with 1 exception [12], the chemotherapeutic response of recurrent LCNEC was as good as that of SCLC [13–15]. In addition, Rossi et al. [15] reported that in another 15 patients treated with NSCLC-based regimens, the response rate was 0 % and the MST was 21 months. In the present study, an objective response was obtained in 4 of 6 LCNEC patients (66 %) who received platinum plus irinotecan or platinum plus etoposide, so-called SCLC-based regimens, and in 9 of 16 possible LCNEC patients (56 %) who received SCLC-based regimens. These results suggest that SCLC-based regimens might be effective for both LCNEC and possible LCNEC. In addition, the present study also indicated that treatment with paclitaxel-containing regimens might be effective for LCNEC and possible LCNEC. These anticancer drugs will be key to the treatment of LCNEC and possible LCNEC.

This study has several limitations. It was a retrospective study with an inherent potential for bias. Collection of clinical characteristics and treatment response data was retrospective and the follow-up interval for physical examinations was indefinite. The sample size was small. Therefore, future studies would benefit from investigating a much larger sample.

In conclusion, no statistically significant differences were found in the response rate, PFS, and OS between the LCNEC and possible LCNEC groups. These results suggest that possible LCNEC is similar to LCNEC in chemotherapeutic efficacy. In the future, a study of a larger series of LCNEC patients is mandatory to confirm the role of chemotherapeutic strategy.

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Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Substantial risk affects the stage-dependent outcomes of cisplatin-based adjuvant chemotherapy for completely resected non-small cell lung cancer

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Abstract
Purpose Effective adjuvant chemotherapy (Adj.C) for completely resected non-small cell lung cancer (NSCLC) was recently established. However, there may be some unresolved adverse effects, as have been observed in early stage populations or long-term survivors after other types of Adj.C. The substantial risk in such patients was examined by a mathematical method.
Methods Variables X and Y were defined by two outcomes of Adj.C: X = the ability to eliminate micro-metastasis and Y = the development of effects that threaten life. Then, the following formula was generated: Survival benefit = (death rate) X − (death rate) X Y − (survival rate) Y. We then solved for X and Y and verified our findings using reported data from clinical trials.
Results By solving two simultaneous equations for the formula applied to the data for stage (1) IA and (2) IIIA in the LACE study (J Clin Oncol 26:5043–5051, 2008), X and Y were 2.6 and 1.9, respectively. When these values were applied in the formula for stage IB patients in the same study, the theoretical (−2.3 %) and reported values (2.5 %) were close. When these were applied for stage IB–IIIA patients in the IALT study (N Engl J Med 350:351–360, 2004), the theoretical (5.0 %) and reported values (4.1 %) were also similar.
Conclusion Assuming a substantial risk provides an explanation for the stage-dependent outcomes of Adj.C for completely resected NSCLC.

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Keywords Non-small cell lung cancer · Surgery · Adjuvant chemotherapy

Introduction

Since its introduction several decades ago, adjuvant chemotherapy (Adj.C) has been hoped to help eliminate latent residual disease in surgically resected non-small cell lung cancer (NSCLC) patients. However, a number of randomized clinical trials that were performed during the 1980's and early 1990's did not show positive results because of the low efficacy of the chemotherapeutic regimens and/or low statistical power of the studies. After a notable meta-analysis was performed by the British Medical Council, which reported a hazard ratio (HR) of 0.87 (P = 0.054) for surgery combined with platinum-based chemotherapy compared to surgery alone [1], large-scale or stage-specific randomized trials were conducted using more sophisticated statistical analyses; some of these results showed significant survival benefits with Adj.C, especially in patients with stage II–III diseases, but not in those with stage I cancers [2–5]. The varying results observed between stages might be explained by two different hypotheses.

One is that tumors of higher-stage disease are more sensitive to cytotoxic chemotherapy compared to tumors of lower-stage disease; however, this hypothesis is inconsistent with the principle that the efficacy of chemotherapy is inversely correlated with the extent of tumor burden or stage [6, 7]. A second hypothesis is that Adj.C rescues patients with micro-metastases, but that it has life-threatening effects for patients who have already been cured by surgery. This hypothesis is supported by the meta-analysis done by the Lung Adjuvant Cisplatin Evaluation (LACE) collaborative group based on recent clinical trials [8].

The LACE study revealed significant adverse effects of adjuvant chemotherapy for stage IA (HR 1.40), no benefit for stage IB (HR 0.93), and significant benefits for stages II and IIIA (HR 0.83 for both) patients. Such stage-dependent outcomes clearly indicate that the balance between benefit and risk is different among disease stages, and that there is no benefit, but only risk, for patients who are cured by surgery alone. More recently, a retrospective analysis of the gene signatures in a clinical trial cohort of BR 10 [9], which was included in the LACE meta-analysis, demonstrated that adjuvant chemotherapy shortened the survival of good risk patients with a hazard risk of 3.3, although Adj.C significantly improved the survival of poor risk patients, with a hazard risk of 0.33. This analysis also suggested that adjuvant chemotherapy was harmful for patients who were cured of lung cancer by surgery alone.

In this study, a substantial risk of Adj.C was hypothesized and verified by a mathematical method using data from previously reported clinical trials.

Materials and methods

This study was based on the hypothesis that there is a substantial, but hidden, risk of Adj.C for certain subgroups of patients. A survival curve based on this hypothesis is illustrated in Fig. 1a. In this figure, each proportion of a particular survival status was denoted as either "died of cancer" (a), "died of Adj.C", "rescued by Adj.C" (d), or "cured by surgery alone" (e). The category "died of Adj.C" was further divided into "not cured by surgery alone (b)" and "cured by surgery alone" (c) (Fig. 1a). To better understand each status, the relationships of these categories with the micro-metastasis status and treatment outcomes are summarized in Fig. 1b.

A survival benefit in terms of 5-year survival is expressed by (d − c) (Fig. 1b). Two variables, X and Y, were hypothesized, respectively, as the potential to eliminate micro-metastasis with Adj.C and the potential for Adj.C to be life-threatening. The values for X and Y were assumed to be constant in each clinical trial, as they were mainly dependent on the chemotherapy regimens used. The relationships between X/Y and a/b/c/d/e are demonstrated in Fig. 2a. With these definitions, the following formula was generated (Fig. 2b):

Survival benefit of Adj.C = Death rate of patients treated with surgery alone · X − Death rate of patients treated with surgery alone · X · Y − Survival rate of patients treated with surgery alone · Y.

Both X and Y were solved from two simultaneous equations that were generated when using reported data for (1) stage IA and (2) stage IIIA patients in the LACE meta-analysis study [8]. The findings were verified using the data for stage IB patients in the LACE study [8] and the International Adjuvant Lung Cancer Trial (IALT) [2], which provided most of the population for the LACE study.

Results

Given the results of the LACE study, values for X and Y were determined. Since the approximate survival rate at 5 years was 75 % for stage IA patients undergoing surgery alone, the 5-year survival rate for an adjuvant therapy group was calculated to be approximately 66 % based on the hazard ratio demonstrated in the LACE study (HR = 1.41). Therefore, based on the formula for a survival benefit, the following equation was generated:

$$25 \cdot X - 25 \cdot X \cdot Y - 75 \cdot Y = 66 - 75$$

$$X = (3Y - 0.36)/(1 - Y)$$

Since the approximate survival rate at 5 years was 25 % for stage IIIA patients after surgery alone, the 5-year survival rate for an adjuvant therapy group was calculated to be approximately 32 % based on the hazard ratio demonstrated in the LACE study (HR = 0.83). Therefore, the next equation was generated to be:

$$75 \cdot X - 75 \cdot X \cdot Y - 25 \cdot Y = 32 - 25$$

$$X = (1/3Y + 0.09)/(1 - Y)$$

Then, solving the above equations simultaneously for X and Y gave: $X = 0.26$ and $Y = 0.19$.

When $X = 0.26$ and $Y = 0.19$ were applied to stage IB patients in the LACE study, the theoretical survival benefit at 5 years was 3.0 %, which was close to the 2.5 % that was calculated based on the reported hazard ratio of 0.92 and the hypothetical 5-year survival rate of 60 % for stage IB patients treated by surgery alone:

$$40 \cdot 0.26 - 40 \cdot 0.26 \cdot 0.19 - 60 \cdot 0.19 = -2.3 \fallingdotseq 2.5 \ (\textit{result from LACE})$$

When X and Y were applied to the data from the IALT study (5-year survival rate for surgery alone for stages IB-IIIA = 40 %) [2], which comprised the largest number of patients included in the LACE meta-analysis, the theoretical value for the survival benefit and the obtained survival benefit were similar, as shown by:

$$(60 \cdot 0.26) - (60 \cdot 0.26 \cdot 0.19) - (40 \cdot 0.19) = 5.0 \fallingdotseq 4.1 \ (\textit{result from IALT})$$

When X and Y were derived from the data from the BR 10 [3] and the Adjuvant Navelbine International Trials Association studies [4], both of which clearly demonstrated stage-dependent benefits of adjuvant chemotherapy, X and Y were 0.79 and 0.26, and 0.56 and 0.25, in the respective

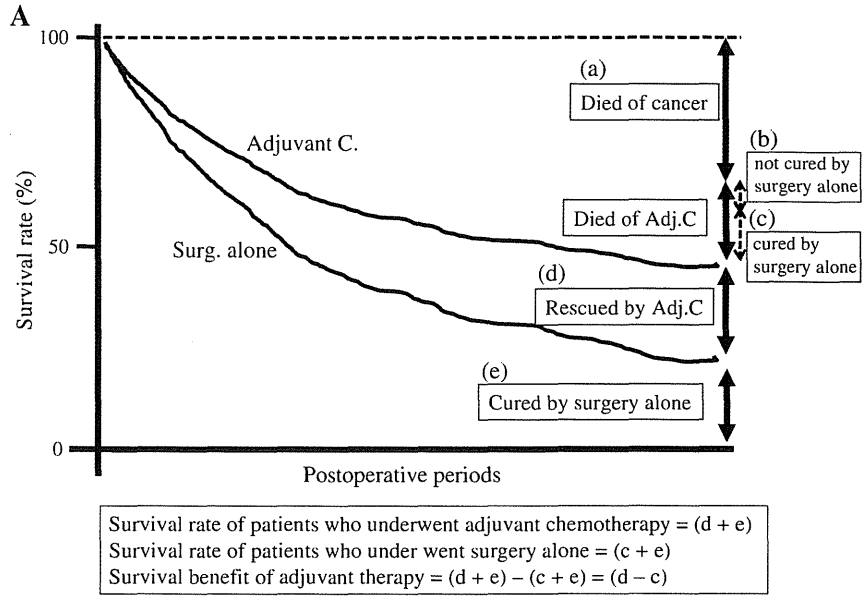

Fig. 1 The concept of a substantial risk of *Adj.C*. **a** A schematic diagram of the survival curves considering a substantial risk of *Adj.C*. **b** The relationships between each patient population, the treatment outcome status and survival data

B

	Negative micro metastasis		Positive micro metastasis	
	No fatal harm of Adj.C	Fatal harm of Adj.C	No fatal harm of Adj.C	Fatal harm of Adj.C
Died of cancer (a)			Ineffective Adj.C	
Died of Adj.C : not cured by surgery alone (b)				
Died of Adj.C : cured by surgery alone (c)				
Rescued by Adj.C (d)			Effective Adj.C	
Cured by surgery alone (e)				

trials. The survival benefits calculated using these values were also similar to the reported values.

Discussion

In this study, I attempted to explain the stage-dependent outcomes of adjuvant cisplatin doublet chemotherapy for NSCLC patients using a simple conceptual formula, which was based on the hypothesis that Adj.C has a substantial fatal risk. If this concept is true in actual practice, the survival benefits of Adj.C recognized in clinical trials can be expressed as follows: (rate of patients who are rescued from recurrence by Adj.C) − (rate of those who suffer from fatal disadvantages of Adj.C although cured by surgery alone), which is described by (d − c) in Fig. 1b.

Based on this hypothesis, the survival benefit becomes negative when (d < c), and Adj.C for stage IA is associated with such a finding. This study demonstrates that this concept matches the reported results of the LACE study [8]. A substantial fatal risk of Adj.C is prominent for patients who are cured by surgery alone, and this would cause the stage-dependent outcomes observed in that study, because these patients included those in all stages, although at various proportions. In other words, the greater the proportion of patients who are cured by surgery alone, the less favorable the outcome of Adj.C will be.

One may argue that the stage-dependent outcome of Adj.C can be attributed to the sensitivity of tumor cells to chemotherapy. Cell cycle-dependent agents are active for rapidly proliferating cells. The disease stage may be associated with the aggressive potential of tumors; if so, it might be consistent that adjuvant chemotherapy is more

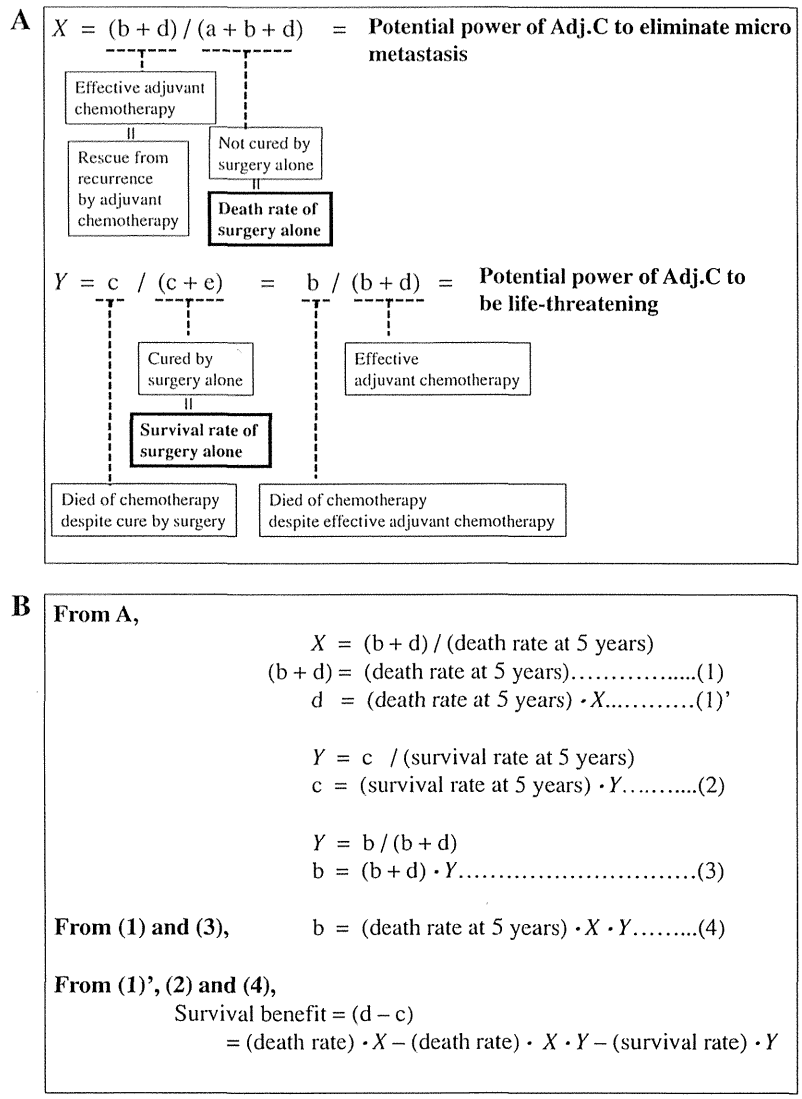

Fig. 2 Relationships among hypothetical variables and real data. **a** Explanations for *X* and *Y* using the patient proportions (*a* to *e*) illustrated in Fig. 1a. **b** The survival benefit is expressed using *X* and *Y*. The procedure for calculation is explained using the variables of patient proportions (*a* to *e*)

active against stage II/IIIA than stage I tumor. However, the negative outcomes of adjuvant chemotherapy for patients with stage IA [8] or with biologically less aggressive tumors [9] cannot be explained only by the chemo-sensitivity of tumors. In addition, *X* (defined as the ability of Adj.C to eliminate micro-metastasis) is not taken into account for patients who are cured by surgery alone.

The theoretical formula used here is simply a model that can be applied to evaluate the use of adjuvant chemotherapy for NSCLC. However, there is a caveat: the NSCLC stage may not be an absolute condition for considering adjuvant chemotherapy, because approximately 20 % of the patients who would be cured by surgery alone may die due to Adj.C using cisplatin-based regimens (Fig. 1a).

From this hypothetical analysis, a reason for the various outcomes of Adj.C among patients with different stages of disease, but with completely resected NSCLC, can be suggested. However, at present, only the disease stage is taken into account when considering the use of adjuvant chemotherapy. Thus, the current treatment paradigm may present a dilemma with regard to "Primum non nocere (First, do no harm)" from the Hippocratic Oath. Thoracic oncologists need to make a better effort to identify the optimal target populations for adjuvant chemotherapy among patients with completely resected NSCLC. Stage-independent prognostic factors may provide an alternative, because these factors could exclude patients from being candidates for Adj.C who would be cured by surgery alone.

There were a number of limitations to this study. First, *X* and *Y* were merely conceptual variables and cannot be applied in real practice. In addition, the elimination of micro-metastasis was assumed to equal survival at 5 years to simplify the concept used in this study. Finally, actual