each society, including the ASCO, NCCN and American College of Radiology (ACR), has established its own guidelines, no uniform method of surveillance following surgery has been established to date [6].

The serum CEA levels are sometimes assessed to monitor the progression of lung cancer following complete resection, although the prognostic significance of the perioperative serum CEA level and the detectability of recurrence during the follow-up period using this marker remain unclear. Therefore, this study was designed to evaluate the significance of measuring the serum CEA level from the preoperative state to the follow-up period for detecting recurrence and estimating survival in completely resected NSCLC patients.

MATERIALS AND METHODS

This study was conducted with the Institutional Review Board of Aichi Cancer Center approval. Between April 2001 and March 2006, 529 patients underwent surgery for NSCLC with curative intent at Aichi Cancer Center. All the patients were without active concomitant malignancies and received regular postoperative follow-up, including measurement of the serum CEA level at every visit. Eleven patients who died or relapsed within 3 months of surgery were excluded from the analysis. Consequently, 518 patients constituted the study population. We retrospectively reviewed the medical records of all the patients and assessed the conditions of cancer recurrence and overall survival (OS). The seventh edition of the tumor node metastasis classification [7] was applied in this cohort, and the pathological diagnosis of the tumour was made based on the World Health Organization classification [8]. An epidermal growth factor receptor (EGFR) mutational analysis of the surgical specimens was performed using one-step reverse transcription-polymerase chain reaction (RT-PCR) amplification with the QIAGEN One-Step RT-PCR Kit (Qiagen, Valencia, CA, USA). The patient characteristics were as follows: the median age was 63 years (range 22–82 years); 299 patients were male and 219 patients were female; 331 tumours were classified as pathological stage I, 88 tumours were classified as pathological stage II and 99 tumours were classified as pathological stage III; 140 tumours were adenocarcinomas (EGFR mutants), 268 tumours were adenocarcinomas (EGFR wild-type) and 110 tumours were of other histological types of NSCLC (Table 1).

The follow-up programme included chest radiography, measurement of the serum CEA level and a physical examination and clinical interview at every visit. The frequency of visits was every 3 months up to 2 years from surgery and every 6 months thereafter. Chest and abdominal computed tomography (CT) scans were obtained annually and non-scheduled radiological examinations, including additional chest and abdominal CT, brain magnetic resonance imaging and positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose combined with CT (PET-CT), were performed depending on the physicians' decision, especially when prominent or continuous elevation of the serum CEA level was observed. With a cut-off value of 5.0 ng/ml, the serum CEA level was classified as elevated or normal. The patients were divided into three groups according to a preoperative serum CEA level (preoperative CEA) and a serum CEA level 1–3 months after surgery (postoperative CEA): those with a normal preoperative CEA and a normal postoperative CEA (N group, $n = 380$), those

Table 1: Clinicopathological characteristics of the patients

	N group ($n = 380$)	HN group ($n = 105$)	H group ($n = 33$)	*P*-value
Median follow-up period, month (range)	69 (6–116)	67 (8–115)	31 (4–110)	<0.001
Median age, years (range)	63 (22–82)	63 (39–79)	67 (56–81)	0.039
Median preoperative CEA, ng/ml (range)	2.1 (0.5–5.0)	9.0 (5.1–286.0)	8.2 (2.6–160.0)	<0.001
Median postoperative CEA, ng/ml (range)	1.6 (0.5–4.9)	3.2 (0.6–4.9)	7.3 (5.3–147.5)	<0.001
Gender, *n*				
Female	174	33	12	0.022
Male	206	72	21	
Smoking status, *n*				
Never	175	28	9	<0.001
Current or former	205	77	24	
Histology, *n*				
Adenocarcinoma (EGFR mutant)	112	24	4	0.109
Adenocarcinoma (EGFR wild-type)	192	54	22	
Other NSCLCs	76	27	7	
Pathological stage, *n*				
I	270	47	14	<0.001
II	56	26	6	
III	54	32	13	
Surgical procedure, *n*				
Pneumonectomy	10	2	0	0.104
Lobectomy	335	100	31	
Sublobar resection	35	3	2	
Perioperative platinum-based chemotherapy, *n*				
No	362	91	30	0.013
Yes	18	14	3	
Patients with recurrence, *n* (%)	122 (32%)	49 (47%)	19 (58%)	0.001
Sensitivity of an elevated follow-up CEA for detecting recurrence	30% (37/122)	82% (40/49)	Not assessed	
Specificity of an elevated follow-up CEA for detecting recurrence	98% (252/258)	73% (41/56)	Not assessed	

CEA: carcinoembryonic antigen; NSCLC: non-small-cell lung cancer; EGFR: epidermal growth factor receptor.

with an elevated preoperative CEA and a normal postoperative CEA (HN group, $n = 105$) and those with an elevated postoperative CEA, regardless of the preoperative CEA (H group, $n = 33$). Postoperative surveillance combined with the follow-up programme was performed until death or for at least 5 years after surgery in all the patients. With at least one record of an elevated serum CEA level during the follow-up >3 months after surgery (follow-up CEA), the follow-up CEA was classified as elevated. The follow-up CEA was not evaluated following recurrence confirmed with radiological evidence. Post-recurrence OS was defined as the interval between the date of first disease recurrence and the date of death or the last follow-up (30 June 2012). The slope of the changes in serum CEA levels was defined as follows: delta CEA = postoperative CEA minus preoperative CEA/preoperative CEA.

Statistical analysis

The χ^2 and Kruskal–Wallis tests were used for comparisons of proportions and continuous values between the three groups (N group, HN group and H group), respectively. OS was defined as the time from surgery to death due to any causes or last follow-up without death. Disease-free survival (DFS) was defined as the time from surgery to relapse or death due to any causes. Post-recurrence survival (PRS) was defined as the time from first recurrence to death due to any causes. For OS, DFS and PRS, the patients without events were censored at the last follow-up date. The Kaplan–Meier method was used to estimate DFS and OS, and the log-rank test was used to compare the survival curves. The multivariate Cox regression analyses were performed to estimate hazard ratios (HRs) and 95% confidence interval (CI) for DFS, OS and PRS. Statistical significance was defined as $P < 0.05$. All analyses were conducted using the JMP software program (version 8.0.1, SAS Institute, Inc., Cary, NC, USA) and SAS 9.3 (SAS Institute, Inc.).

RESULTS

The clinicopathological characteristics of the patients stratified by the serum CEA level are given in Table 1. The patients in the

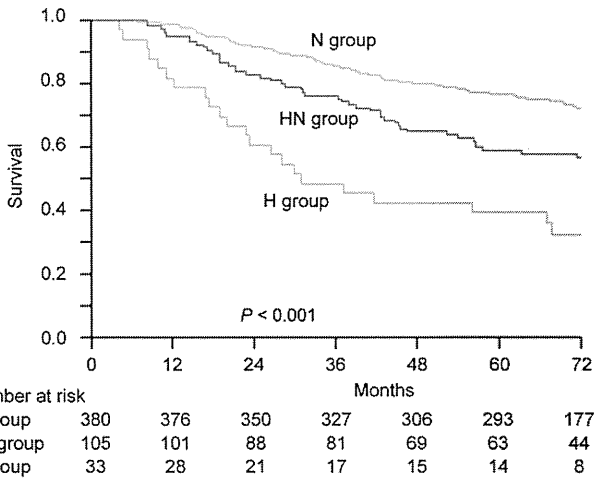

Figure 1: Overall survival curves of the CEA groups.

Table 2: Correlations between elevated serum CEA levels and the clinicopathological characteristics of the patients with recurrence

	N group		HN group		H group	
Preoperative CEA	Normal		Elevated		Normal or elevated	
Postoperative CEA	Normal		Normal		Elevated	
Follow-up CEA	Elevated (*n*)	Normal (*n*)	Elevated (*n*)	Normal (*n*)	Elevated (*n*)	Normal (*n*)
Total	37	85	40	9	19	0
Gender						
Female	12	30	13	2	6	0
Male	25	55	27	7	13	0
Smoking status						
Never	13	27	13	1	7	0
Current or former	24	58	27	8	12	0
Histology						
Adenocarcinoma (EGFR mutant)	13	25	12	1	3	0
Adenocarcinoma (EGFR wild-type)	20	32	20	3	14	0
Other NSCLCs	4	28	8	5	2	0
Pathological stage						
I	19	34	9	1	5	0
II	3	23	13	4	4	0
III	15	28	18	4	10	0
Site of first recurrence (numbers include multiple responses)						
Lung	12	37	9	3	6	0
Lymph node	10	29	16	3	5	0
Bone	11	13	9	1	7	0
Brain	6	14	11	2	1	0
Pleura	8	7	2	1	5	0
Liver	2	2	5	0	2	0
Adrenal gland	1	2	1	0	0	0

CEA: carcinoembryonic antigen; NSCLC: non-small-cell lung cancer; EGFR: epidermal growth factor receptor.

N group were more frequently female and never-smokers and more likely to have pathological stage I disease than the patients in the other groups. No significant differences were observed in histology or surgical procedures between the three groups. Among 140 patients with adenocarcinoma and EGFR mutations, 78 patients were female and 62 patients were male, 89 patients were never-smokers and 51 patients were current or former smokers.

The 5-year OS was 87% for patients with stage I disease, 57% for patients with stage II disease and 30% for patients with stage III disease ($P < 0.001$). One hundred and twenty-two patients (32%) in the N group, 49 patients (47%) in the HN group and 19 patients (58%) in the H group developed recurrence. The site of first recurrence was the lungs in 67 patients, lymph nodes in 63 patients, bone in 41 patients, brain in 34 patients, pleura in 23 patients, liver in 11 patients, adrenal glands in 4 patients and other in 8 patients (these numbers include multiple responses). Among the patients with recurrence, 78 (64%) of 122 patients in the N group, 31 (63%) of 49 patients in the HN group and 7 (37%) of 19 patients in the H group developed recurrence at an asymptomatic stage. The sensitivity and specificity of an elevated follow-up CEA for detecting recurrence were 30 and 98% in the N group and 82 and 73% in the HN group, respectively. The 5-year DFS and OS were 66 and 77% in the N group, 49 and 59% in the HN group and 36 and 39% in the H group, respectively (Fig. 1).

The correlations between elevated follow-up CEA and the clinicopathological characteristics among the patients with recurrence are given in Table 2. In the HN group, most patients ($n = 40$, 82%) exhibited recurrence in association with an elevated follow-up

Table 3: Correlation between an elevated serum CEA level and the site of first recurrence in the HN group

Mode of presentation	Asymptomatic		Symptomatic	
Preoperative CEA	Elevated		Elevated	
Postoperative CEA	Normal		Normal	
Follow-up CEA	Elevated (*n*)	Normal (*n*)	Elevated (*n*)	Normal (*n*)
Total	27	4	13	5
Site of first recurrence (numbers include multiple responses)				
Lung	8	3	1	0
Lymph node	14	1	2	2
Bone	6	1	3	0
Brain	5	0	6	2
Pleura	0	0	2	1
Liver	3	0	2	0
Adrenal gland	1	0	0	0

CEA: carcinoembryonic antigen.

Table 4: Multivariate Cox regression analysis including the three groups (N group, HN group and H group)

	Disease free survival			Overall survival			Post-recurrence survival		
	HR	95% CI	*P*-value	HR	95 %CI	*P*-value	HR	95% CI	*P*-value
Group									
N	1.000			1.000			1.000		
HN	1.145	0.825–1.589	0.419	1.132	0.798–1.606	0.488	1.060	0.720–1.561	0.766
H	2.202	1.387–3.496	0.001	2.346	1.448–3.800	0.001	1.206	0.665–2.187	0.537
Histology									
Adenocarcinoma (EGFR mutant)	1.000			1.000			1.000		
Adenocarcinoma (EGFR wild-type)	0.782	0.555–1.102	0.161	1.060	0.728–1.544	0.762	1.699	1.115–2.588	0.014
Other NSCLCs	0.840	0.546–1.291	0.427	1.007	0.629–1.612	0.978	1.515	0.900–2.553	0.118
Age	1.012	0.995–1.030	0.159	1.018	1.000–1.037	0.056	1.006	0.987–1.026	0.536
Gender									
Female	1.000			1.000			1.000		
Male	1.249	0.850–1.835	0.258	1.258	0.822–1.925	0.290	0.999	0.638–1.566	0.998
Smoking status									
Never	1.000			1.000			1.000		
Current or former	1.167	0.770–1.769	0.466	1.305	0.833–2.046	0.245	1.057	0.666–1.678	0.813
Pathological stage									
I	1.000			1.000			1.000		
II	3.036	2.084–4.425	<0.001	3.036	2.027–4.548	<0.001	1.604	0.986–2.609	0.057
III	7.115	5.071–9.983	<0.001	6.396	4.453–9.188	<0.001	1.455	0.956–2.214	0.080
Perioperative platinum-based chemotherapy									
No	1.000			1.000			1.000		
Yes	0.637	0.389–1.046	0.075	0.853	0.508–1.433	0.547	1.431	0.818–2.503	0.210
Procedure									
Pneumonectomy	1.000			1.000			1.000		
Lobectomy	0.815	0.372–1.785	0.610	0.760	0.321–1.797	0.532	0.596	0.203–1.753	0.348
Sublobar resection	0.938	0.357–2.464		1.012	0.357–2.865	0.982	0.960	0.274–3.359	0.949
Site of first recurrence									
Others							1.000		
Only lung							0.722	0.455–1.146	0.167
Mode of presentation									
Asymptomatic							1.000		
Symptomatic							2.330	1.583–3.429	<0.001

DFS: disease-free survival; OS: overall survival; PRS: post-recurrence survival; CEA: carcinoembryonic antigen; NSCLC: non-small-cell lung cancer; EGFR: epidermal growth factor receptor; HR: hazard ratio; CI: confidence interval.

CEA. No differences were observed in gender, smoking status, histology or pathological stage. Table 3 shows the correlations between the follow-up CEA, mode of presentation (asymptomatic or symptomatic) and clinicopathological characteristics in the HN group. Twenty-seven cases of recurrence were detected at an asymptomatic stage in association with an elevated follow-up CEA.

The multivariate Cox regression analyses of DFS, OS and PRS including the 3 groups (N group, HN group and H group) are given in Table 4. The H group had a significantly worse prognostic factor for DFS and OS.

The multivariate Cox regression analysis including the preoperative and postoperative value of CEA as continuous variable is given in Table 5. The postoperative CEA was a statistically significant prognostic factor for OS and PRS, while that was a marginally significant prognostic factor for DFS.

The median delta CEA was −0.29 (range: −0.99 to 5.48). In the multivariate Cox regression analysis, the delta CEA was not a significantly prognostic factor for DFS (HR 1.088, $P = 0.430$) and OS (HR 1.170, $P = 0.100$), but was a marginally prognostic factor for PRS (HR 1.234, $P = 0.051$). Limited to the patients with an elevated preoperative CEA (>5.0 ng/ml, $n = 133$), the delta CEA had a significantly prognostic value for DFS (HR 1.702, $P = 0.002$), OS (HR 1.789, $P < 0.001$) and PRS (HR 1.607, $P = 0.004$).

Regarding the PRS of patients with recurrence ($n = 190$), the presence of EGFR wild-type adenocarcinoma and symptoms at the time of recurrence were significant prognostic factors (Tables 4 and 5).

DISCUSSION

In 1981, the National Institutes of Health reported that the preoperative serum CEA level is correlated with the stage of cancer and prognosis [9]. With respect to lung cancer, Yoshimasu *et al.* [10] reported that assessing the time course of changes in the serum CEA level following surgery is useful for predicting the prognosis. Furthermore, several investigators have reported that grouping patients based on the serum CEA level before and 1–3 months after surgery is correlated with postoperative survival among pathological stage I NSCLC patients [11–14]. We categorized the patients into three groups for the current analysis in an almost similar way to that used in these studies. The average half-life of serum the CEA level following resection of lung cancer has been reported to be ~7 days [15]. Therefore, several weeks are required after surgery in order to evaluate the postoperative serum CEA level at a certain plateau determined by the elimination and production of CEA.

In this study, results indicate that a preoperative CEA does not have significant influence on survival (DFS, OS and PRS), whereas a postoperative CEA does. This suggests that a preoperative CEA is primarily associated with stage of disease, while an elevated postsurgical serum CEA level was found to be correlated with occult CEA-producing tumours that recurred in spite of resection. Evaluation of a postoperative CEA and/or a delta CEA would have the potential to be one of the indicators for adjuvant chemotherapy.

Table 5: Multivariate Cox regression analysis including the preoperative and postoperative CEA as continuous variable

	Disease free survival			Overall survival			Post-recurrence survival		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Preoperative CEA	1.001	0.995–1.006	0.802	0.997	0.991–1.003	0.351	0.993	0.987–1.000	0.050
Postoperative CEA	1.010	0.999–1.021	0.066	1.019	1.008–1.031	0.001	1.018	1.005–1.032	0.008
Histology									
Adenocarcinoma (EGFR mutant)	1.000			1.000			1.000		
Adenocarcinoma (EGFR wild-type)	0.851	0.603–1.200	0.357	1.232	0.846–1.795	0.277	1.960	1.301–2.954	0.001
Other NSCLCs	0.875	0.568–1.349	0.546	1.083	0.674–1.742	0.741	1.631	0.970–2.743	0.065
Age	1.014	0.997–1.031	0.108	1.021	1.003–1.040	0.024	1.010	0.990–1.029	0.327
Gender									
Female	1.000			1.000			1.000		
Male	1.222	0.825–1.810	0.316	1.300	0.846–1.998	0.231	1.030	0.661–1.605	0.896
Smoking status									
Never	1.000			1.000			1.000		
Current or former	1.209	0.797–1.833	0.372	1.322	0.844–2.071	0.223	1.087	0.689–1.715	0.719
Pathological stage									
I	1.000			1.000			1.000		
II	3.062	2.096–4.472	<0.001	3.107	2.075–4.653	<0.001	1.734	1.072–2.807	0.025
III	7.174	5.129–10.033	<0.001	6.765	4.708–9.720	<0.001	1.681	1.107–2.552	0.015
Perioperative platinum-based chemotherapy									
No	1.000			1.000			1.000		
Yes	0.690	0.423–1.123	0.135	0.916	0.549–1.527	0.735	1.400	0.813–2.410	0.225
Procedure									
Pneumonectomy	1.000			1.000			1.000		
Lobectomy	0.887	0.407–1.935	0.764	0.849	0.361–1.993	0.706	0.648	0.220–1.909	0.431
Sublobar resection	0.977	0.373–2.562	0.962	1.072	0.380–3.024	0.896	0.998	0.284–3.506	0.998
Site of first recurrence									
Others							1.000		
Only lung							0.721	0.453–1.149	0.169
Mode of presentation									
Asymptomatic							1.000		
Symptomatic							2.473	1.693–3.612	<0.001

DFS: disease-free survival; OS: overall survival; PRS: post-recurrence survival; CEA: carcinoembryonic antigen; NSCLC: non-small-cell lung cancer; EGFR: epidermal growth factor receptor; HR: hazard ratio; CI: confidence interval.

Regarding the role of measuring the follow-up CEA in the N group, the sensitivity of an elevated follow-up CEA for detecting recurrence was only 30%. We analysed the patients' clinicopathological backgrounds in order to distinguish between recurrent patients with and those without an elevated follow-up CEA. Although Shoji *et al.* [16] reported an association between an elevated serum CEA level and EGFR mutations in patients with recurrent lung adenocarcinoma, our results in the N group did not match this finding. The EGFR mutation status, gender and smoking status were not associated with an elevated follow-up CEA in the patients with recurrence in the N group ($P = 0.533$, 0.759, 0.716, respectively). It was difficult to establish clinicopathological criteria for identifying the small number of patients in the N group who might gain benefits from measuring the serum CEA level during the follow-up period. Measuring the serum CEA level in the N group seemed to have little value, except for the high specificity.

In the HN group, both high sensitivity and specificity of an elevated follow-up CEA for detecting recurrence were observed. The number of patients whose recurrence was detected in association with an elevated follow-up CEA in an asymptomatic stage was 27 (55%) from among 49 patients. This result indicates the value of measuring the serum CEA level during the follow-up period for detecting recurrence in the HN group.

The primary aim of providing intensive follow-up is to improve survival by detecting postoperative recurrence at an asymptomatic stage. Many investigators and patients believe it is important to correctly diagnose recurrence as early as possible. Westeel *et al.* [1] reported that detecting recurrence at an asymptomatic stage using scheduled procedures during intensive follow-up resulted in a good prognosis in a prospective non-randomized study. In contrast, Walsh *et al.* [2] and Younes *et al.* [3] reported that the early detection of lung cancer recurrence simply generates a lead time bias, and whether it offers any survival benefits is questionable. In the current clinical guidelines for surveillance, the American College of Chest Physicians (ACCP), NCCN and ACR recommend the use of a follow-up programme including chest CT, whereas the ASCO does not due to the lack of proven value of such programmes [6]. As to the limitations of this retrospective study, whether the early detection of asymptomatic recurrence following measurement of the serum CEA level during the follow-up provides survival benefits remains unclear.

The other limitation of this study is that some patients had an originally elevated serum CEA level due to, for example, smoking and the evaluation of the serum CEA level in these patients did not precisely reflect the amount of lung cancer.

According to Virgo *et al.* [17], due to the desire to please patients and avoid malpractice suits, thoracic surgeons are motivated to continue surveillance following surgery, resulting in improvement of the patient's quality of life. Although there remains room for debate regarding whether measuring the serum CEA level ~14 times for each patient during a 5-year follow-up is cost-effective, we believe that this simple method has the potential to achieve trusting relationships with patients, consequently maintaining their quality of life.

In conclusion, this study provides important information regarding the significance of measuring the serum CEA levels in completely resected NSCLC patients. Measuring the serum CEA level during the follow-up period is useful in patients in whom an elevated serum CEA level normalizes after surgery, and the serum CEA level 1–3 months after surgery is, therefore, considered to have prognostic value for estimating survival.

Conflict of interest: none declared.

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Surgery for Small Cell Lung Cancer

A Retrospective Analysis of 243 Patients from Japanese Lung Cancer Registry in 2004

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Introduction: Indications for surgical resection for small cell lung cancer (SCLC) have been very limited. Because early-stage SCLC is a rare presentation of lung cancer, studies comparing surgical resection among a large number of patients are unlikely to be conducted. This study reports the most recent surgical outcomes of a large number of SCLC patients who underwent surgery in 2004.Methods: In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study regarding the prognosis and clinicopathologic profiles of 11,663 patients who underwent resection for primary lung cancer in 2004. Of the 11,663 patients, 243 patients with SCLC (2.1%) were included in this study. The registry data of the patients with SCLC were analyzed, and the clinicopathologic profiles and surgical outcomes of the patients were evaluated.Results: The 5-year survival rate for all cases (n = 243, 213 males, mean age 68.2 years) was 52.6%. The 5-year survival rates by c-stage and p-stage were as follows: IA, 64.3% (n = 132) and 72.3% (n = 93); IB, 45.7% (n = 36) and 61.1% (n = 51); IIA, 50.5% (n =25); and 44.8% (n = 27); IIB, 33.3% (n = 10) and 40.3% (n = 17); IIIA, 30.5% (n = 30) and 23.4% (n = 45); and IV, 0% (n = 7) and 0% (n = 9), respectively. A multivariate analysis showed that the significant prognostic factors were age, gender, c-stage, and surgical curability. A kappa value was moderate conformity between c-stage and p-stage in all cases.Conclusions: Surgical resection in selected patients with early-stage SCLC, especially stage I, had favorable results.

Key Words: Small cell lung cancer, Surgery, Registry

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Lung cancer is the leading cause of cancer-related death in the United States and in Japan. Small cell lung cancer (SCLC) represents only 13–20% of all lung cancers.[1] It is distinguished by its rapid growth rate and early dissemination to regional lymph nodes and distant sites. Therefore, SCLC represents less than 5% of cases in large surgical series.[2]

In 1973, the Medical Research Council[3] reported a postoperative survival rate that was as poor as the survival rate for nonsurgical treatment in SCLC patients. In addition, Mountain[4] reported that there was no difference in outcome between resected and non-resected cases in 368 SCLC patients. After those two studies were published, the standard treatment for SCLC became chemotherapy and/or radiation, and surgery was basically contraindicated. In 1983, the Lung Cancer Study Group[5] initiated the only randomized trial of adjuvant surgical resection after induction chemotherapy. This trial failed to show improved survival rates after surgery compared with radiation after neoadjuvant chemotherapy. Thereafter, several authors reported rather favorable surgical results in a relatively small number of patients with early-stage SCLC.[6,7] Shepherd and colleagues[8] reported in 1988 that the postoperative 5-year survival rate was 31% in 77 patients with surgery as the primary treatment for SCLC. In 2005, Japan Clinical Oncology Group reported a 68% 3-year postoperative survival rate in patients with resected clinical stage I SCLC undergoing postoperative adjuvant chemotherapy.[9] Recently, several large cohort studies of surgery for limited disease SCLC have

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been reported.[10,11] An analysis of 205 clinical stage IA SCLC patients from the National Cancer Institute's Surveillance Epidemiology and End Results database who underwent radical lobectomy showed a 5-year survival rate of 50.3% without postoperative adjuvant radiotherapy.[12]

However, optimal indications for surgical resection for SCLC and the efficacy of perioperative chemotherapy have not yet been determined. Because early-stage SCLC is a rare presentation, accounting for 2.4% to 3.4% of resected lung cancer,[13] and a definite preoperative diagnosis of cell type as SCLC is rather difficult, studies prospectively comparing the significance of surgical resection in a large number of cases are unlikely to be conducted.

This study aimed to investigate recent surgical results for SCLC patients retrospectively, based on the large-volume Japanese nationwide registry database.

PATIENTS AND METHODS

Patients

In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study regarding the prognoses and clinicopathologic profiles of 11,663 patients who underwent resection for primary lung cancer in 2004. Of those patients, 243 with histologically confirmed SCLC (2.1%) were extracted from the database. The clinicopathologic factors and their relationship to postoperative survival were evaluated.

The following items were included for analysis: gender, age, smoking status, serum tumor markers (carcinoembryonic antigen and proGRP), clinical tumor, node, metastasis (TNM) stage (c-stage), pathological TNM stage (p-stage), surgical procedure, surgical curability (R0 and R1/R2), presence or absence of preoperative and postoperative chemotherapy, and survival time. The Union for International Cancer Control TNM staging, version 7,[14] was adopted in this study.

This study and the Japanese Joint Committee of Lung Cancer Registry registration study adhere to the Ethical Guidelines for Epidemiologic Research imposed by the Japanese Ministry of Health, Labor, and Welfare.[15]

Statistical Analysis

Survival time was defined as the time from the date of the surgery to the date of the last follow-up. Survival curves were estimated by the Kaplan-Meier method. Differences in survival were assessed by the log-rank test. A multivariate analysis by Cox's proportional hazards model was used to test the significance of prognostic factors. Statistical significance was considered to be established when the associated p value was less than 0.05.

A kappa value of conformity between c-stage and p-stage was also determined.[16] A kappa has a maximum of 1 (indicating perfect agreement) and a minimum −1 (indicating worse than chance agreement). A value of 0 indicates an agreement that is no better than chance, values above 0.4 are usually considered indicative of "moderate" agreement, and values higher than 0.6 are considered "good" agreement.

RESULTS

Patient Profiles

The clinicopathologic characteristics of the 243 patients with resected SCLC are summarized in Table 1. Of the 243 patients with resected SCLC, there were 213 (87.7%) men and 30 (12.3%) women. The mean age at the time of operation was 68.2±9.5 years. Preoperative serum proGRP levels were elevated in 58 patients (23.9%) and within normal limits in 185 (76.1%) patients. The major operative mode was lobectomy/bilobectomy (n = 174, 71.6%), followed by segmentectomy/wedge resection (n = 51, 21.0%). More than 60% of patients (n = 169, 68.6%) were diagnosed as c-stage IA or IB. As for the pathologic stage, 93 patients (38.3%) were recognized as p-stage IA, and 51 (21.0%) as p-stage IB. There were 45 (18.5%) patients in p-stage IIIA. Complete resections (R0) were achieved in 214 (88.1%) patients.

Postoperative Survival

The overall postoperative survival curve is shown in Figure 1. The 5-year survival rate of the 243 patients with SCLC was 52.6%. The postoperative survival curves according to c-stage and p-stage are shown in Figure 2. The 5-year survival rates by c-stage and p-stage were as follows: 64.3% in c-stage IA, 45.7% in c-stage IB, 50.5% in c-stage IIA, 33.3% in c-stage IIB, 30.5% in c-stage IIIA, 0% in c-stage IV, 72.3% in p-stage IA, 61.1% in p-stage IB, 44.8% in p-stage IIA, 40.3% in p-stage IIB, 23.4% in p-stage IIIA, and 0% in p-stage IV. The differences in survival were significant between c-stage IA and c-stage IB (p = 0.0423), c-stage IA and c-stage IIB (p = 0.0367), c-stage IA and IIIA (p = 0.0023), p-stage IA and p-stage IIA (p = 0.0074), p-stage IA and p-stage IIB (p = 0.0033), p-stage IA and p-stage IIIA (p = 0.0000), and p-stage IB and p-stage IIIA (p = 0.0006).

The relationship of each factor to survival, determined by univariate analysis, is shown in Table 1. Except for c-stage and p-stage, there was statistical significance in gender (women fared better than men did), serum ProGRP level (worse in elevated cases), and surgical curability (R0 patients fared better than R1/R2 patients did). In a Cox proportional hazards model to predict overall survival, the following factors persisted as significant prognostic factors: gender, age, c-stage, and surgical curability (Table 2).

Clinicopathological Results According to c-Stage

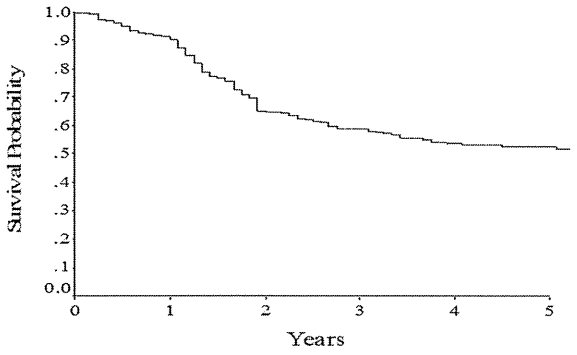
The relationship of p-stage, perioperative chemotherapy, and surgical curability to c-stage is shown in Table 3. In c-stage IA + IB, 39 of 168 cases (23.2%) were upstaged to p-stage, and eight of 30 cases (26.7%) in c-stage IIIA and two (66.7%) of three in c-stage IIIB were downstaged to p-stage I or II. A conformity of c-stage and p-stage was determined to be moderate, with a kappa value of 0.425.

As for surgical curability, in c-stage I (IA + IB), 158 cases (96.3%) underwent R0 resection and only six cases (3.7%) underwent R1/R2 resection. In c-stage II, 32 cases

TABLE 1. Characteristics of Patients with Resected Small Cell Lung Cancer and Overall Survival

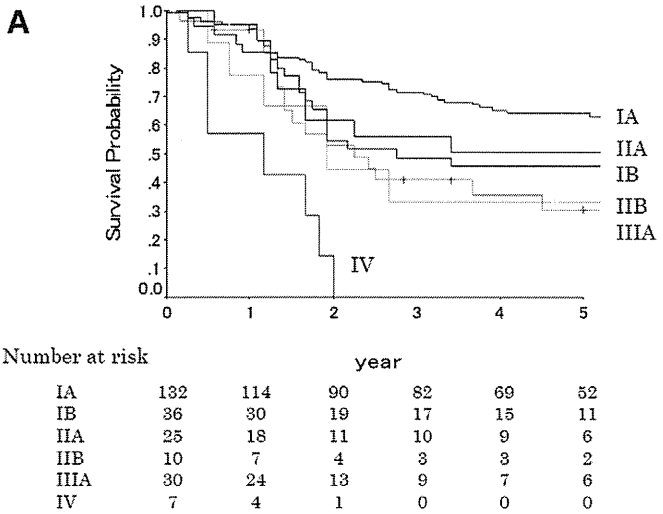
	N (%)	5-Year Survival (%)	Comparison	*p* Value
Gender				
Men	213 (87.7)	49.3		0.0190
Women	30 (12.3)	79.0		
Smoking				
Nonsmoker	22 (9.1)	41.6		
Ex-smoker	74 (30.5)	50.8	Nonsmoker vs. ex-smoker	0.5740
Smoker	124 (51.0)	56.3	Nonsmoker vs. smoker	0.2253
Unknown	23 (9.5)			
Operative mode				
Wedge resection	37 (15.2)	30.6	Wedge resection vs. lobectomy/bilobectomy	0.0019
Segmentectomy	14 (5.8)	63.6	Segmentectomy vs. lobectomy/bilobectomy	0.7848
Lobectomy/ bilobectomy	174 (71.6)	58.3		
Pneumonectomy	9 (3.7)	31.8	Pneumonectomy vs. lobectomy/bilobectomy	0.1600
Unknown	9 (3.7)			
c-stage				
IA	132 (54.3)	63.3		
IB	36 (14.3)	45.7	IB vs. IA	0.0423
IIA	25 (10.3)	50.5	IIA vs. IA	0.2531
IIB	10 (4.1)	33.3	IIB vs. IA	0.0367
IIIA	30 (12.3)	30.5	IIIA vs. IA	0.0023
IIIB	3 (1.2)	—	—	—
IV	7 (2.9)	0	IV vs. IA	0.0000
p-stage				
IA	93 (38.3)	72.3		
IB	51 (21.0)	61.1	IB vs. IA	0.1855
IIA	27 (11.1)	44.8	IIA vs. IA	0.0074
IIB	17 (7.0)	40.3	IIB vs. IA	0.0033
IIIA	45 (18.5)	23.4	IIIA vs. IA	0.0000
IIIB	1 (0.4)	—	—	—
IV	9 (3.7)	0	IV vs. IA	0.0000
Preoperative treatment				
Done	27 (11.1)			
None	215 (88.5)			
Unknown	1 (0.4)			
Adjuvant chemotherapy				
Done	158 (65.0)	52.0		0.5535
None	69 (28.4)	51.8		
Unknown	16 (6.6)			
Tumor marker				
CEA higher level	70 (28.8)	49.1		0.5631
CEA normal level	173 (71.2)	53.9		
ProGRP higher level	58 (23.9)	36.0		0.0482
ProGRP normal level	185 (76.1)	57.2		
Residual tumor				
R0	214 (88.1)	57.0		0.0000
R1/R2	23 (9.5)	10.2		
Unknown	6 (2.5)			

(94.1%) underwent R0 resection and three cases (8.8%) underwent R1/R2. In c-stageIIIA, R0 resections were done in 19 cases (65.5%). The 5 year survival rates of the patients who underwent R0 resection with c-stage IA, c-stage IB, and c-stage II (IIA+IIB) were 65.4%, 51.6%, and 44.4%, respectively.



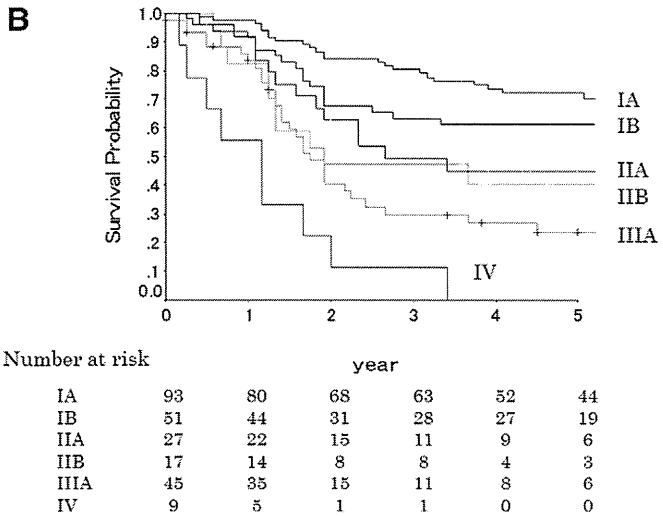
Number at risk 243 201 140 122 100 78

FIGURE 1. Overall survival curve. The 5-year survival rate of patients with small cell carcinoma was 52.6%.



Number at risk

IA	132	114	90	82	69	52
IB	36	30	19	17	15	11
IIA	25	18	11	10	9	6
IIB	10	7	4	3	3	2
IIIA	30	24	13	9	7	6
IV	7	4	1	0	0	0



Number at risk

IA	93	80	68	63	52	44
IB	51	44	31	28	27	19
IIA	27	22	15	11	9	6
IIB	17	14	8	8	4	3
IIIA	45	35	15	11	8	6
IV	9	5	1	1	0	0

FIGURE 2. Overall survival curve based on clinical stage (Union for International Cancer Control-TNM Ver. 7). The 5-year survival rates by c-stage (*A*) and p-stage (*B*) were as follows: IA, 64.3% ($n = 132$) and 72.3% ($n = 93$); IB, 45.7% ($n = 36$) and 61.1% ($n = 51$); IIA, 50.5% ($n = 25$) and 44.8% ($n = 27$); IIB, 33.3% ($n = 10$) and 40.3% ($n = 17$); IIIA, 30.5% ($n = 30$) and 23.4% ($n = 45$); and IV, 0% ($n = 7$) and 0% ($n = 9$), respectively.

DISCUSSION

This study, which included 243 patients who underwent surgery in 2004, is the largest in number of patients with SCLC who underwent surgical intervention within just 1 year. It was expected that there would be low variations in preoperative staging evaluation, surgical technique, and postoperative care for each case. For such occasions, the results of this study were meaningful.

The current standard treatment for patients with SCLC is chemotherapy and radiotherapy, except for a portion of early-stage patients. The MRC study[3] in 1973 was a randomized trial, comparing surgery versus radiation alone. In that study, the median survival rate in the surgery group was 6.5 months, compared with 10 months in the radiation group ($p = 0.04$). After that article was published, the standard care was changed from surgical resection to radiotherapy. However, only 34 of the 71 patients (48%) who were enrolled in the surgery arm actually underwent surgical resection. Most of the patients in the MRC study had relatively advanced disease.

Recently, several authors have reported positive results for surgery in patients with early-stage SCLC.[17,18] Shah and colleagues[19] reported on surgical resection for SCLC patients without adjuvant chemotherapy in 1992. Of 28 patients who underwent surgical resection, 14 had stage I disease, five had stage II disease, and nine had stage III disease. The actual 5-year survival rate for patients in stage I was 57.1%, whereas no patients with stage II disease survived 5 years. In half of the patients in Shah's study, the tumor was in a central position. Lim and colleagues[11] reported excellent survival rates for patients in stages I to III who underwent lung resection with nodal dissection for SCLC. A total of 59 patients in their study underwent complete R0 resection for SCLC between 1980 and 2006, and the overall 5-year survival rate was 52%. That study supports the need to reevaluate surgery as the primary treatment and the use of clinical Tumor, Node, Metastasis criteria in the selection of patients with very limited SCLC for surgery. Weksler and colleagues[20] analyzed patients in the Surveillance Epidemiology and End Results database, making a retrospective analysis of a large national database. That study examined 3566 patients with stage I or II SCLC who underwent surgery from 1988 to 2007. Patients with stage II SCLC who had a lung resection had a median survival time of 25.0 months, compared with 14.0 months in patients with stage II SCLC who did not undergo lung resection ($p < 0.0001$). Weksler's study concluded that surgical resection as a component of treatment for stage I or stage II SCLC is associated with significantly improved survival and should be considered in the management of early-stage SCLC.

The overall 5-year survival rate of the patients in our study was 52.6%. Multivariate analysis found that good prognostic factors for survival were younger age, female gender, early-stage disease, and achieved curative resection. The same trends have been previously reported.[11,20] Even though c-stage was one of the most important prognostic factors, the survival rate of the selected patients with c-stage II was favorable results. In particular, patients who underwent complete resection had good survival rates, not only with c-stage I, but also with c-stage II, compared with previous reports. In c-stage

I and II, 190 patients (95.5%) underwent R0 resection, and only nine underwent R1/R2 resection. Surgery was recommended for the c-stage I SCLC patients; however, based on these results, surgical resection might also be considered for patients with stage II SCLC.

On the other hand, in several patients in this study, c-stage did not correspond well with p-stage. Among the patients with stage I SCLC according to preoperative evaluations, 23.2% of the cases were upstaged to stage II or stage III postoperatively. A kappa value demonstrated moderate conformity between c-stage and p-stage in all cases. Vallieres and colleagues[10] reported the same trend when comparing clinical and pathological staging of SCLC, using the International Association for the Study of Lung Cancer database. The overall concordance between clinical and pathologic TNM staging was 58%. When grouping clinical stages I and II together, 19.7% were upstaged to stage pIIIA or above after resection according to the International Association for the Study of Lung Cancer database. Although there is no data on preoperative staging modality in the current study, intensive staging before considering surgical therapy is important, using such tools as positron emission tomography-computed tomography (PET-CT),[21] endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA),[22] and surgical mediastinoscopy.[23]

Large cell neuroendocrine carcinoma (LCNEC) of the lung is defined as a high-grade neuroendocrine tumor no less than SCLC in the 1999 World Health Organization classification of lung tumors.[24] Takei et al.[25] reported that 44% (24 of 55) of operated patients who were originally diagnosed with SCLC (before 1999) were reclassified as LCNEC after the pathologic review. Studies on treatment of patients with SCLC naturally included many cases of LCNEC before LCNEC had been recognized. Thus, it is necessary to be aware when comparing studies performed before and after LCNEC was defined. The subjects of the current study are patients who were operated on in 2004, when LCNEC was well recognized.

In the present study, the survival benefit of postoperative adjuvant chemotherapy was not proved. It is assumed that because of biases in treatment acceptance, the patients' backgrounds were varied, although an analysis was conducted only in p-stage I patients.

Limitations of this analysis include that it is a retrospective study; there is no randomization for adjuvant treatment; there is a lack of preoperative histopathological diagnosis data; there is a lack of information regarding preoperative staging methods; and there is no information regarding the aim of the preoperative treatment and whether the induction treatment was followed by surgery or salvage surgery.

TABLE 2. Multivariate Analysis of Overall Survival for Resected Small Cell Lung Cancer; Cox Proportional Hazards Model

	Hazard Ratio	95% CI	*p* Value
Age, per year increase	1.038	1.015–1.062	0.001
Gender			
Men	1.00		
Women	0.356	0.142–0.893	0.028
c-stage			0.029
IA	1.00		
IB	1.421	0.811–2.493	0.220
IIA	1.298	0.618–2.727	0.491
IIB	2.389	0.986–5.788	0.054
IIIA	1.514	0.797–2.876	0.205
IIIB	3.739	0.863–16.204	0.078
IV	4.557	1.769–11.741	0.002
Tumor marker			
ProGRP normal level	1.00		
ProGRP higher level	1.232	0.774–1.961	0.378
Residual tumor			
R0	1.00		
R1/R2	2.288	1.208–4.332	0.011

CI, confidence interval

CONCLUSION

Surgical resection for selected patients with early-stage SCLC, especially stage I, had good survival outcomes. Based on this result, surgery might also be considered in c-stage II SCLC. Further, a clinical trial on the surgery for patients with c-stage II SCLC was recommended.

TABLE 3. Relationships Between c-Stage, p-Stage, Surgical Curability, and Perioperative Treatment

		p Stage							Surgical Curability[a]	
		IA	IB	IIA	IIB	IIIA	IIIB	IV	R0	R1/2
c-stage	IA	80	23	10	8	11	0	0	126	3
	IB	4	21	3	1	6	0	1	32	3
	IIA	5	2	11	2	4	1	0	21	3
	IIB	0	2	1	4	2	0	1	10	0
	IIIA	4	2	0	2	21	0	1	19	10
	IIIB	0	1	1	0	0	0	1	3	0
	IV	0	0	1	0	1	0	5	3	4

R0, no residual tumor; R1/R2, microscopic or macroscopic residual tumor.
[a]Six patients data of curability were missing.

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Abstract Majority of cases of lung cancer are detected at an advanced stage; such patients are usually treated with chemotherapy and radiotherapy, and the prognosis is frequently poor. Surgical resection remains the only reliable curative method for the treatment of lung cancer, and combined resection of the primary tumor and involved neighboring structures is performed when possible in patients with locally advanced disease. In the TNM classification, tumors with direct extrapulmonary extension are subdivided based on the anatomic extent of disease and its potential for surgical treatment: T3 lesions with limited, circumscribed extension are thought to be potentially surgically resectable, whereas T4 tumors with extensive extension are considered unresectable. Although surgical treatment for T3 lesions is generally accepted, the outcome is frequently not satisfactory. On the other hand, advanced surgical techniques are now being applied for T4 lesions due to improvements in surgery and anesthesiology and progress in combined treatment modalities. In the present staging, T4N0–1M0 lesions are categorized as stage IIIA disease, and T4 tumors without mediastinal nodal metastasis are now considered to be potentially curable if complete resection is possible. This article reviews the modern surgical management of patients with lung cancer invading neighboring structures, including the chest wall, superior sulcus, diaphragm, tracheal carina, left atrium, superior vena cava, aorta and vertebrae. Furthermore, the surgical treatment of carcinomatous pleuritis, which was categorized as T4 disease in the previous TNM classification, is also assessed, and the role of surgical resection in cases of locally advanced lung cancer is discussed.

Keywords Lung cancer · Locally advanced disease · Surgical treatment · Combined resection

Introduction

Lung cancer is the leading cause of cancer death worldwide [1]. Surgical resection remains the gold standard for curative treatment of early-stage lung cancer. Although patients are often diagnosed with advanced disease at presentation, surgical management is employed in cases of selected locally advanced T3 and T4 disease. According to a report of a nationwide registry study of surgical lung cancer cases during 2004, which was conducted by the Japanese Joint Committee of Lung Cancer Registry, 8.7 % of patients underwent combined resection of involved neighboring structures [2].

T3 lesions with limited, circumscribed extrapulmonary extension are thought to be potentially surgically resectable, whereas T4 tumors with extensive extrapulmonary extension are considered unresectable. However, the Union for International Cancer Control revised the TNM staging in the seventh edition published in 2009; that is, T4N0–1M0 lesions, which were classified as stage IIIB disease in the sixth edition, are now categorized as stage IIIA disease [3]. This modification indicates that T4 tumors without mediastinal nodal metastasis are potentially curable if complete resection is possible. Although carcinomatous pleuritis is now classified as M1a and stage IV disease, this condition was categorized as T4 disease in the

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previous TNM classification and several results of the surgical treatment have been reported to date.

Therefore, we herein review the modern surgical management of locally advanced non-small cell lung cancer including carcinomatous pleuritis, with reference to the involved organs, and discuss the role of such treatment.

Chest wall

In 1947, Coleman first reported the curative treatment with pneumonectomy and simultaneous block resection of the chest wall for primary carcinoma of the lung with invasion of the ribs [4]. Since then, surgical treatment for lung cancer with chest wall invasion has been reported with acceptable morbidity and mortality rates.

Table 1 shows the recently reported outcomes of patients treated with surgical resection for lung cancer with chest wall invasion [5–8]. Complete resection and lymph node metastasis have been reported to be implicit prognostic factors in patients with such locally advanced lung cancer, whereas the depth of invasion and extent of combined resection remain controversial. A few investigators have emphasized the routine application of en bloc resection of the lung and ribs, regardless of the depth of chest wall invasion, from the viewpoint of obtaining a safe margin [9, 10], while others have recommended the use of extrapleural resection for lung cancer with invasion limited to the parietal pleura due to the lower morbidity and mortality rates [5, 6, 11]. Extrapleural resection is generally selected in cases of lung cancer with shallow invasion limited to the parietal pleura, and the high rate of complete resection demonstrates that experienced surgeons are able to make a correct judgment regarding the extent of combined resection during surgery in such cases. Consequently, patients with N0–1 disease are considered to be good candidates for surgical treatment, which is required to achieve complete resection with a negative surgical margin. Furthermore, combined resection of the chest wall has been shown to be a very high-risk procedure in elderly patients [6].

The surgical methods used for chest wall resection are common and non-specific. In general, detachment from the chest wall is first performed in order to avoid congestion of the lung to be excised. It is essential to maintain an adequate margin from the tumor when cutting the ribs. The indications of and methods for chest wall reconstruction vary among institutions. Generally, the indication for reconstruction is as follows: a large defect of caudal chest wall, which area is not covered with scapula, including resection of more than three ribs or measuring at least 4.0 × 4.0 cm in area. Weyant et al. [12] emphasized that the incidence of respiratory failure in their series was lower than that previously reported, which may be related to their routine use of a rigid prosthesis for reconstruction of large, anteriorly or laterally located defects causing a flail chest.

Concerning perioperative therapy, lung cancer with chest wall invasion is mostly staged as IIB or IIIA disease; therefore, the administration of adjuvant chemotherapy after surgical resection is recommended in many modern guidelines. On the other hand, a few reports have been published regarding the efficacy of induction therapy for lung cancer with chest wall invasion, whereas preoperative chemoradiotherapy has become a standard strategy for treating superior sulcus tumors (SSTs). In patients with chest wall invasion, we have conducted a phase II study, the Central Japan Lung Study Group Trial 0801, under the hypothesis that induction chemoradiotherapy followed by surgery can improve the prognosis such as in patients with SST [13].

Superior sulcus

SSTs or apical chest tumors, sometimes referred to as Pancoast tumors, were first described by a radiologist, Pancoast [14]. These tumors are located in the apex of the thoracic cavity and often detected at an advanced stage. Due to their anatomical location, involvement of the surrounding structures, such as the brachial plexus, subclavian vessels and/or spine, is usually observed in association with involvement of the first rib. Therefore,

Table 1 Surgical outcomes of patients with lung cancer involving the chest wall

Investigator	Year	No. of patients	Complete resection (%)	Operative mortality (%)	5-Year survival (%)			
					N0	N1	N2	All patients
Downey [5]	1999	269	65	5.7	49[a]	27[a]	15[a]	32[a]
Magdeleinat [6]	2001	201	83	7.0	25[a]	20[a]	21[a]	21 (24[a])
Doddoli [7]	2005	309	100	7.8	40	24	8	31
Kawaguchi [8]	2012	407	86	NR	49	36	21	43

NR not reported

[a] The data indicate 5-year survival rates of patients with complete resection of the tumor

this disease was considered a contraindication for surgery until Chardack and Maccallum [15] reported the case of a long-term survivor treated with en bloc resection of the right upper lobe, chest wall and nerve roots followed by adjuvant radiotherapy. Subsequently, the strategy of applying induction radiation at a dose of 30–35 Gy followed by surgery with curative intent was introduced by Shaw et al. [16]. The standard treatment strategy for SST remained unchanged for approximately 30 years until trimodality therapy consisting of induction chemoradiation followed by surgical resection was developed.

Based on the findings of recent reports, as shown in Table 2, concurrent chemoradiotherapy prior to resection has become the standard treatment for resectable SST [17–20]. The Southwest Oncology Group and Japan Clinical Oncology Group both conducted prospective phase II studies of induction chemoradiation followed by surgery in SST patients and reported significantly superior results with respect to the rates of complete resection and survival compared to that observed in the previous literature, despite the use of a multi-institutional setting [18, 19]. Candidates for the trimodality therapy are thought to include patients with N0–1 or ipsilateral N3 (supraclavicular) disease and/or T3–4 tumors, such as those with tumor invasion to the subclavian vessels, Th1 and C8 nerve roots or spine, when potentially resectable.

The surgical approach is the most interesting aspect with respect to the treatment of SST due to anatomical difficulties. The standard approach of creating a higher posterolateral incision for SST invading the middle or posterior compartments of the thoracic inlet was first reported by Shaw et al. [16]. Dartevelle et al. [21] later reported the use of the anterior approach to treat subclavian vessels exhibiting tumor involvement, and the evolution of surgical treatment, particularly that employing the anterior approach, was ignited. Other surgical approaches for SST have been reported by a number of thoracic surgeons [22–25], and the appropriate approach should be selected according to the locoregional extension of the tumor [26].

Pericardium

A few studies have assessed tumors invading the pericardium, and patients with such tumors have been reported to generally have a worse prognosis (Table 3) [8, 27, 28]. However, due to the small number of patients, the current results remain equivocal. Because prognostic factors have not yet been determined, the optimal operative indications for patients with tumor invading the pericardium remain an open question.

En bloc resection of the pericardium along with the tumor is usually possible. At the time of pericardial resection, it is necessary to obtain a sample of the pericardial effusion for a cytological examination. If malignant findings are observed, resection must be abandoned. Following resection of the pericardium, reconstruction may be performed using non-absorbable material to prevent cardiac herniation, if necessary.

Diaphragm

Because lung cancer involving the diaphragm is also rare, only a few reports with a relatively small number of cases have been published concerning the surgical treatment of patients with these tumors (Table 4) [8, 27, 29, 30]. The frequency of diaphragmatic invasion of lung cancer is extremely low, at 0.3–0.4 % [8, 29, 30].

Patients with N0 disease are considered to be good surgical candidates. Because the number of patients with N1 disease totaled less than 20 in all previous reports, it remains controversial whether to recommend surgery in such cases. Incomplete resection of lung cancer with diaphragmatic involvement offers no curative benefits. In patients with complete resection, combined resection of other organs has been reported to have an adverse effect on survival [30].

En bloc resection of the diaphragm along with the tumor should be attempted whenever possible. Generally, more than 2 cm of the macroscopically uninvolved diaphragm is excised from all tumor borders. If the defect

Table 2 Surgical outcomes of patients with superior sulcus tumor

Investigator	Year	No. of patients	Complete resection (%)	Operative mortality (%)	Chemotherapy	Radiation dose (Gy)	Pathological complete response (%)	5-Year survival (%)
Kwong [17]	2005	36	97	2.7	CDDP based	57	41	59 (2-Year survival)
Rusch [18]	2007	110	76	2.3	CDDP + etoposide	45	36	44
Kunitoh [19]	2008	76	68	2.0	MVP	45	21	56
Kappers [20]	2011	19	100	2.0	CDDP	66	53	33

CDDP cisplatin, *MVP* mitomycin + vindesine + cisplatin

Table 3 Surgical outcomes of patients with lung cancer involving the pericardium

Investigator	Year	No. of patients	Complete resection (%)	Operative mortality (%)	5-Year survival (%)			
					N0	N1	N2	All patients
Sakakura [27]	2008	14	79	NR	NR	NR	NR	21
Riquet [28]	2010	32	81	15.6	NR	NR	NR	15
Kawaguchi [8]	2012	20	NR	NR	50	80	38	54

NR not reported

Table 4 Surgical outcomes of patients with lung cancer involving the diaphragm

Investigator	Year	No. of patients	Complete resection (%)	Operative mortality (%)	5-Year survival (%)			
					N0	N1	N2	All patients
Rocco [29]	1999	15	93	0	27	0	0	20
Yokoi [30]	2000	63	87	1.6	28[a]	20[a]	0	19 (23[a])
Sakakura [27]	2008	12	75	NR	NR	NR	NR	33
Kawaguchi [8]	2012	31	NR	NR	55	0	19	43

NR not reported

[a] The data indicate 5-year survival rates of patients with complete resection of the tumor

Table 5 Surgical outcomes of patients with lung cancer involving the main bronchus within 2 cm of the carina

Investigator	Year	No. of patients	Complete resection (%)	5-Year survival (%)			
				N0	N1	N2	All patients
Riquet [34]	2002	68	76	NR	NR	NR	35
Sakakura [27]	2008	33	85	NR	NR	NR	49
Kawaguchi [8]	2012	45	NR	92	46	36	55

NR not reported

area in the diaphragmatic muscle is smaller than the size of a fist, it is possible to perform direct suturing with non-absorbable bladed sutures. In cases of large defects, diaphragmatic reconstruction using non-absorbable material may be necessary to prevent herniation of the abdominal organs.

Trachea, carina and main bronchus

Lung cancer sometimes lies in the main bronchus within 2 cm of the carina (T3 lesions) and/or involves the trachea or carina (T4 lesions). Surgical intervention for these lesions requires challenging techniques for thoracic surgeons.

Main bronchus within 2 cm of the carina

Pneumonectomy and sleeve lobectomy are conducted for the surgical treatment of tumors located in the main bronchus within 2 cm of the carina [31]. In order to avoid pneumonectomy, which results in a substantial loss of the lung function and quality of life, bronchoplastic techniques combined with various surgical methods, such as pulmonary artery reconstruction, have been performed [32]. The operative mortality for sleeve lobectomy is approximately 2 % [33]. The modern surgical outcomes for T3 tumors invading the central main bronchus are shown in Table 5 and appear to be superior to those of other T3 tumors [8, 27, 34].

Trachea and carina

Surgical treatment for tumors with tracheal and/or carinal invasion has been performed using sleeve pneumonectomy and tracheocarinal resection. Encouraging results have been reported in recent series, in particular an excellent survival rate in pN0 patients (Table 6) [35–39]. Patients with N2 involvement exhibit a poor prognosis, even when treated with aggressive surgical resection. The long-term survival has been reported to be influenced by the pathologic nodal status and completeness of resection, not age, sex or pre- or postsurgical oncologic treatment [39]. The operative mortality has recently been reported to be 3–8 % [36, 38, 39], which is similar to that noted for conventional pneumonectomy, ranging from 5 to 15 %.

Right sleeve pneumonectomy is the most common procedure for treating these tumors, and the safe limit of

Table 6 Surgical outcomes of patients with lung cancer involving the trachea and carina

Investigator	Year	No. of patients	Complete resection (%)	Operative mortality (%)	5-Year survival (%)			
					N0	N1	N2	All patients
Mitchell [35]	2001	60	85	15	51	32	12	42
Regnard [36]	2005	65	94	7.7	38		5.3	27
de Perrot [37]	2006	119	94	7.6	53		15	44
Yıldızeli [38]	2008	92	90	6.5	50		17	43
Eichhorn [39]	2013	64	83	3.1	70	35	9	31

resection is approximately 4 cm between the lower trachea and left main bronchus [40]. A variety of carinal resection and reconstruction procedures have been performed according to the tumor characteristics in practice, and the use of careful patient selection and anesthetic and surgical techniques is advocated in order to minimalize morbidity and mortality [41].

Left atrium

The optimal management of patients with lung cancer invading the left atrium remains controversial. Nevertheless, some tumors have occasionally been removed, with reported 5-year survival and operative mortality rates of 14–30 and 0–10 %, respectively (Table 7) [42–46]. The survival rates are less favorable than those associated with resection of other T4 structures. The nodal status, type of operation and completeness of resection have been found to have a significant impact on survival [45, 46]. Therefore, in carefully selected NSCLC patients with left atrium invasion, candidates for surgical resection are only those with N0–1 disease.

Although combined resection of the lung and left atrium is performed using vascular clamps, cardiopulmonary bypass (CPB) is required in cases of intraluminal polypoid tumor growth. However, as reported in the literature, the application of CPB has only rarely been used [45] and is frequently avoided [42–44]. In patients with right tumors, the Sondergaard technique is useful for lengthening the left atrial cuff [44].

Table 7 Surgical outcomes of patients with lung cancer involving the left atrium

Investigator	Year	No. of patients	Complete resection (%)	Operative mortality (%)	5-Year survival (%)
Tsuchiya [42]	1994	44	NR	NR	22
Ratto [43]	2004	19	58	0	14
Spaggiari [44]	2005	15	100	0	39 (3-Year survival)
Kuehnl [45]	2010	35	69	9	16
Stella [46]	2012	31	94	10	30

NR not reported

Table 8 Surgical outcomes of patients with lung cancer involving the superior vena cava

Investigator	Year	No. of patients	Complete resection (%)	Operative mortality (%)	5-Year survival (%)
Shargall [48]	2004	15	93	14	57 (3-Year survival)
Suzuki [49]	2004	40	70	10	24
Spaggiari [50]	2007	52	NR	8	31
Yıldızeli [38]	2008	39	85	8	29

NR not reported

Superior vena cava

Lung cancer with invasion of the superior vena cava (SVC) has been considered to be a contraindication for surgery [47]. However, over the last 20 years, several reports regarding the surgical resection in selected patients have shown improved results, with acceptable perioperative morbidity, mortality and 5-year survival rates (Table 8) [38, 48–50].

Which type of SVC resection and reconstruction is performed depends on the degree of venous involvement [50]. Following partial SVC resection, the pattern of reconstruction includes the use of simple running sutures, vascular staplers or patch replacement. In cases of SVC infiltration of more than 50 % of the circumference of the vessel, total prosthetic replacement of the SVC is required using an extraluminal shunt placed between the left brachiocephalic vein and the right atrium and the cross-clamping technique.

Suzuki et al. [49] identified SVC invasion by metastatic lymph nodes to be a significant poor prognostic factor. On the other hand, several studies have reported that the lymph node status and completeness of resection do not

significantly affect survival [38, 48]. Clinically, among carefully selected NSCLC patients with SVC invasion, candidates for surgical resection are considered to include those with N0–1 disease and the potential for complete resection [51].

Aorta

Aortic involvement by lung cancer has long been considered to be a relative contraindication for surgical resection. However, in recent years, the publication of several reports regarding aortic resection and replacement has increased interest in the application of extended procedures. Among studies focusing specifically on aortic resection, the overall 5-year survival rate has been reported to be 17–48 %, with an operative mortality of 0–13 % (Table 9) [52–55]. The encouraging long-term survival rates obtained in patients with N0 disease and complete resection are essential in selected patients with aortic involvement.

The type of aortic resection depends on the degree of tumor involvement and consists of subadventitial dissection and aorta en bloc resection and reconstruction. In cases in which segmental resection of the descending aorta is necessary, partial cardiopulmonary bypass between the femoral vein and artery or temporary bypass grafting from the ascending to the descending aorta is used. Recently, some reports have shown that pulmonary resection with combined resection of the aortic wall can be successfully accomplished after thoracic aorta endovascular stent graft placement without the use of cardiopulmonary bypass support [56, 57]. The placement of an endovascular stent is an alternative in selected patients with aortic invasion.

Spine

Lung cancer that invades to the spine is classified as T4 disease, which has long been considered to be unresectable. However, due to the development of innovative approaches for performing vertebral resection and spinal reconstruction and the combined use of multimodality therapy since the late of 1980s, low mortality with encouraging 5-year survival rates of 31–61 % has been reported in several series (Table 10) [58–61].

Table 9 Surgical outcomes of patients with lung cancer involving the aorta

Investigator	Year	No. of patients	Complete resection (%)	Operative mortality (%)	5-Year survival (%)
Ohta [52]	2005	16	75	13	48
Shiraishi [53]	2005	16	50	13	17
Mithos [54]	2007	13	100	0	31
Wex [55]	2009	13	85	0	45

Surgery alone is almost never an adequate treatment for this disease and must be combined with other modalities. Recently, the introduction of concurrent chemoradiation prior to surgery for SST, which often exhibits upper spinal involvement, has been reported to yield relatively favorable rates of complete resection and overall survival [18, 62].

There are several thoughts as to the resection technique for performing vertebrectomy. The technique introduced by Grunenwald et al. [63] involves en bloc total vertebrectomy, in which the transmanubrial approach [24] is used, followed by the creation of a posterior midline incision. After performing laminectomy one level above and below the tumor, the vertebral body is rotated into the chest toward the tumor and subsequently removed en bloc along with the lung and chest wall. Anraku et al. [64] introduced their 'staged surgery' for multiple-level total vertebrectomy based on the principle of en bloc resection. Recently, long-term favorable outcomes of this procedure were reported, with a 5-year survival rate of 61 % in 48 patients [61]. The authors also reported that the response to induction therapy was found to be an independent prognostic factor in a multivariate analysis.

Carcinomatous pleuritis

Carcinomatous pleuritis in patients with lung cancer is usually found to accompany frank malignant pleural effusion and is associated with a short-term survival [65]. The present TNM classification categorizes this condition as M1a and stage IV disease and suggests that patients with carcinomatous pleuritis are candidates for non-surgical treatment. However, this disorder is sometimes discovered with or without a small amount of pleural effusion during thoracotomy in patients with resectable lung cancer, with a reported incidence of 1.5–4.5 % [66–68]. Surgical treatment has been applied in affected patients at some institutions, achieving long-term survival in selected cases [66–70]. On the other hand, the outcome of chemotherapy for patients with pleural dissemination detected during surgery was recently reported, and the result was more favorable than that of patients with preoperatively diagnosed stage IV disease [71]. Therefore, a part of carcinomatous pleuritis could be considered as a locally advanced disease.

The surgical procedures employed are diverse, including limited resection, lobectomy, pneumonectomy and extrapleural pneumonectomy. The median postoperative survival time and 5-year survival rate have been reported to be

Table 10 Surgical outcomes of patients with lung cancer involving the spine

Investigator	Year	No. of patients	Vertebrectomy		Multilevel (%)	Complete resection (%)	5-Year survival (%)
			Total	Hemi			
Grunenwald [58]	2002	19	4	15	3 (16)	79	14
Schirren [59]	2011	20	4	16	18 (90)	80	47
Fadel [60]	2011	54	5	49	54 (100)	91	31
Collaud [61]	2013	48	10	38	47 (98)	88	61

Table 11 Surgical outcomes of patients with lung cancer and carcinomatous pleuritis

Investigator	Year	No. of patients	Median survival (months)		5-Year survival (%)		
			N0–1	N2	N0–1	N2	All patients
Ichinose [66]	2001	100	21		NR	NR	23
Mordant [67]	2011	32	15		NR	NR	16
Okamoto [68]	2012	73	30		NR	NR	24
Yokoi [70]	2013	23	126	21	61	6	34

NR not reported

17–30 months and 13–24 %, respectively (Table 11) [66–68, 70]. We performed extrapleural pneumonectomy in 23 patients between 1988 and 2012, with a median survival time and 5-year survival rate of 34 months and 34 %, respectively [69, 70]. Among 12 patients with pathologic N0–1 disease, six remain alive without disease at four to 288 months after surgery, for a median survival time and 5-year survival rate of 126 months and 61 %, respectively. These results indicate that carefully selected patients with carcinomatous pleuritis may be candidates for surgical treatment including extrapleural pneumonectomy.

Nevertheless, at present, with the progression of chemotherapy and molecular targeted therapy, a few reports of the outcomes of patients with carcinomatous pleuritis detected during surgery are available [71]. Therefore, the appropriate treatment strategy for patients with minimal pleural carcinomatosis should be investigated.

Conclusion

Locally advanced lung cancer with involvement of the neighboring structures is usually treated with chemotherapy and radiotherapy, with the exception of T3N0–1M0 tumors. However, promising outcomes of surgical treatment have been reported in selected patients with more advanced T4 tumors, and the TNM classification has been revised according to these results. Furthermore, due to improvements in surgical techniques and perioperative management as well as progress in the development of combined treatment modalities, such as radiotherapy and chemotherapy including molecular targeted therapy, it is now possible to administer more aggressive multidisciplinary treatment. Therefore, the criteria for selecting candidates for surgical treatment of lung cancer involving the neighboring structures should be reevaluated.

Conflict of interest The authors declare no conflict of interest.

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