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Original Article

The Role of Adjuvant Therapy Following Surgical Resection of Small Cell Lung Cancer: A Multi-Center Study

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Purpose This multi-center, retrospective study was conducted to evaluate the long-term survival in patients who underwent surgical resection for small cell lung cancer (SCLC) and to identify the benefit of adjuvant therapy following surgery.

Materials and Methods The data of 213 patients who underwent surgical resection for SCLC at four institutions were retrospectively reviewed. Patients who received neoadjuvant therapy or an incomplete resection were excluded.

Results The mean patient age was 65.29±8.93 years, and 184 patients (86.4%) were male. Lobectomies and pneumonectomies were performed in 173 patients (81.2%), and 198 (93%) underwent systematic mediastinal lymph node dissections. Overall, 170 patients (79.8%) underwent adjuvant chemotherapy, 42 (19.7%) underwent radiotherapy to the mediastinum, and 23 (10.8%) underwent prophylactic cranial irradiation. The median follow-up period was 31.08 months (interquartile range, 13.79 to 64.52 months). The 5-year overall survival (OS) and disease-free survival were 53.4% and 46.9%, respectively. The 5-year OS significantly improved after adjuvant chemotherapy in all patients (57.4% vs. 40.3%, p=0.007), and the survival benefit of adjuvant chemotherapy was significant in patients with negative node pathology (70.8% vs. 39.7%, p=0.004). Adjuvant radiotherapy did not affect the 5-year OS (54.6% vs. 48.5%, p=0.458). Age (hazard ratio [HR], 1.032; p=0.017), node metastasis (HR, 2.190; p < 0.001), and adjuvant chemotherapy (HR, 0.558; p=0.019) were associated with OS.

Conclusion Adjuvant chemotherapy after surgical resection in patients with SCLC improved the OS, though adjuvant radiotherapy to the mediastinum did not improve the survival or decrease the locoregional recurrence rate.

Key words Small cell lung carcinoma, Adjuvant chemotherapy, Survival

Introduction

Small cell lung cancer (SCLC) accounts for 13% of all lung cancer diagnoses [1]. The prognosis of patients with SCLC is poor even in those with limited disease owing to rapid progression and the potential for widespread metastases [2,3]. The platinum-based chemotherapy has been the cornerstone of therapy in advanced SCLC, and immune checkpoint inhibitors with chemotherapy have made significant improvements in extensive-stage SCLC recently. Although benefits of surgical resection for SCLC were not found in randomized studies [4,5], a favorable 5-year overall survival (OS) of 30%-50% has been reported in retrospective studies of patients who underwent surgical resection for stage I SCLC [6-10]. Lobectomy followed by adjuvant chemotherapy was associated with significantly longer survival than concurrent chemoradiotherapy (CCRTx) in early and locally advanced SCLC [11]. The current guidelines recommend surgical resection with adjuvant chemotherapy for node-negative T1-2 and selected T3 SCLC [12]. However, less than 5% of patients with SCLC are surgical candidates [13]. Furthermore, a significant under-utilization of surgical treatment for this population has been reported [9].

Despite the introduction of the TNM staging system to

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SCLC [14], the Veterans Administration Lung Group staging system continues to be used, suggesting that surgical treatment has not been routinely implemented in practice. Furthermore, data supporting adjuvant treatments following surgery for SCLC are scarce due to the rarity of the disease and insufficient clinical studies regarding adjuvant treatments. While current guidelines recommend adjuvant chemotherapy, radiotherapy to the mediastinum, and prophylactic cranial irradiation (PCI) [12], only 59% of patients underwent adjuvant treatment after surgery [15]. The practice guidelines have not been uniformly adopted, especially those regarding adjuvant radiotherapy [16]. Though several studies have reported survival benefits for adjuvant therapy [15,17], the benefits of adjuvant radiotherapy and PCI remain controversial [18]. Due to the lack of data supporting optimal adjuvant treatments for surgically-treated SCLC, this study aimed to evaluate the long-term survival in patients who underwent surgical resection for SCLC and to identify the benefits of adjuvant treatment (including adjuvant chemotherapy and radiotherapy) following surgery based on data from large-volume tertiary centers.

Materials and Methods

1. Patients

Patients who underwent a curative surgical resection for SCLC between 2000 and 2017 at four tertiary institutions in South Korea were identified (S1A Fig.). Patients who underwent incomplete resection (n=12) or neoadjuvant treatment (n=35) were excluded from this study.

The patients' pathologic stages were reported according to the eighth TNM staging system [3]. All patients were preoperatively evaluated via contrast chest computed tomography (CT), abdominal CT, whole body bone scan, brain magnetic resonance imaging, or whole-body positron emission tomography–CT based on each institution's polices. The extent of mediastinal lymph node dissection was defined based on the European Society of Thoracic Surgeons [19]. Sixty patients (28.1%) underwent mediastinal lymph node evaluation, including mediastinoscopy or endobronchial ultrasound.

Locoregional recurrence was defined as recurrence at the surgical resection margin or the ipsilateral hilar or mediastinal lymph nodes. Distant metastases were defined as recurrence in N3 lymph nodes, an ipsilateral lobe, the contralateral lung, outside of the thorax, or pleural or pericardial

Table 1. Patient characteristics

Variable	Value
Age (yr)	65.29±8.93
Male sex	184 (86.4)
Clinical T category	
T1/T2/T3/T4	110 (51.8)/91 (42.7)/8 (3.6)/4 (1.9)
Clinical N category	
N0/N1/N2/N3	160 (75.1)/32 (15.0)/20 (9.4)/1 (0.5)
Pathologic T category	
T1/T2/T3/T4	89 (41.8)/95 (44.6)/25 (11.7)/4 (1.9)
Pathologic N category	
Nx/N0/N1/N2/N3	5 (2.3)/125 (58.7)/46 (21.6)/36 (16.9)/1 (0.5)
Extent of resection	
Wedge resection	26 (12.2)
Segmentectomy	14 (6.6)
Lobectomy or bilobectomy	158 (74.2)
Pneumonectomy	15 (7.0)
Mediastinal lymph node dissection	
Systematic MLND	198 (93.0)
Less than systematic MLND	15 (7.0)
Numbers of dissected lymph nodes	25.70±12.88
Operative mortality	4 (1.8)
Adjuvant chemotherapy	170 (79.8)
Adjuvant radiotherapy	42 (19.7)
Prophylactic cranial irradiation	23 (10.8)

Values are presented as mean±standard deviation or number (%). MLND, mediastinal lymph node dissection.

seeding. Follow-up evaluations with chest CT and physical examination were performed every 3 to 6 months based on each institution's policy. OS was calculated from the date of surgery to the last follow-up date (the date of death or last contact). Disease-free survival (DFS) was calculated from the date of surgery to the date of death, recurrence, or last contact. The duration of freedom from recurrence was calculated from the date of surgery to the first date of radiologic evidence of recurrence. Patients who did not die or have recurrence were censored at the last follow-up date.

2. Statistical analysis

Continuous variables were compared using the student's t test, and categorical variables were compared using the chi-square test or Fisher exact test. The median follow-up time was estimated using the reverse Kaplan-Meier method. Patient survival was compared according to the treatment strategies using the log-rank test. A multivariable analysis for survival was performed using the Cox proportional hazard model. The covariates included age, sex, tumor size, pathologic T category, presence of lymph node metastasis, extent of resection (anatomical resection vs. wedge resection), intraoperative mediastinal lymph node evaluation (systematic mediastinal lymph node dissection vs. others), adjuvant chemotherapy, adjuvant radiotherapy, and PCI. Estimates for the hazard function were made from right-censored data using kernel-based methods [20]. A discretization of the time axis was applied in 6 month units. All statistical tests were two-sided with the significance level set at 0.05 and were performed using SPSS ver. 25.0 (IBM Corp., Armonk, NY) and R software ver. 3.3.0 with the "muhaz" package (R Foundation for Statistical Computing, Vienna, Austria).

Results

1. Patient characteristics

The patients' characteristics are summarized in Table 1. The mean patient age was 65.29±8.93 years, and 184 patients (86.4%) were male. Fifty-three patients (24.9%) were clinically diagnosed as node-positive. Lobectomy (including bilobectomy), pneumonectomy, segmentectomy, and wedge resection were performed in 158 (74.2%), 15 (7.0%), 14 (6.6%), and 26 (12.2%), respectively. One hundred ninety-eight patients (93%) underwent a systematic mediastinal lymph node dissection. Overall, 43 patients (20.2%) experienced complications including prolonged air leakage (n=14), postoperative pneumonia (n=6), arrythmia (n=6), postoperative acute respiratory distress syndrome (n=5), vocal cord palsy (n=4), and others (n=8). Four patients (1.8%) died, including two with postoperative acute respiratory distress syndrome, one with massive postoperative bleeding, and one with an early recurrence after operation. Overall, 170 patients (79.8%) underwent adjuvant chemotherapy, 42 (19.7%) underwent radiotherapy to the mediastinum, and 23 (10.8%) underwent PCI (S1B Fig.).

2. Patterns of recurrence and OS

The median follow-up period was 31.08 months (interquartile range, 13.79 to 64.52 months). Sixty-seven patients (31.4%) had recurrence, including 21 (9.8%) with local recurrence, 54 (25.4%) with distant recurrence, and 8 (3.8%) with combined recurrence. The sites of locoregional recurrence were the mediastinal lymph nodes (n=12), lungs (n=4), stumps (n=3), and pleural seeding (n=2). The most frequent distant metastatic sites were the brain (n=19) and liver (n=10).

The 5-year OS and DFS were 53.4% (Fig. 1A) and 46.9%, respectively. The 5-year OS was significantly different between patients with different pathologic N category SCLC (5-year OS among patients with pN0, pN1, pN2, and pN3 SCLC was 62.8%, 51.0%, 24.9%, and 0%, respectively). The 5-year OS was not significantly different between patients with different clinical N category SCLC or pathologic T category SCLC (Fig. 1B and C). The 5-year OS in patients with pathologic stage I, II, and III SCLC were 63.8%, 51.2%, and 31.3%, respectively (stage I vs. III, $p < 0.001$; stage II vs. III, $p=0.006$). The recurrence hazard curve for the first recurrences is illustrated in Fig. 1D. The first recurrence peaked at approximately 10 months postoperatively.

The 5-year OS in patients with cN0pN0, cN0pN+, and cN+pN+ SCLC were 61.4%, 37.6%, and 46.3%, respectively (S2A Fig.). The 5-year OS was significantly different between patients with cN0pN0 SCLC and those with cN0pN+ ($p=0.009$). The 5-year OS in patients who received no adjuvant therapy, adjuvant chemotherapy only, adjuvant radiotherapy only, and adjuvant chemotherapy with radiotherapy (either concurrent or sequential) were 33.4%, 60.5%, 66.7%, and 47.9%, respectively (S2B Fig.). The 5-year OS was significantly different between patients who received no adjuvant therapy and those who received adjuvant chemotherapy ($p=0.001$).

3. Role of adjuvant chemotherapy

Adjuvant chemotherapy was administered in 170 patients (79.8%). Four to six cycles of cisplatin or carboplatin with etoposide was the predominant chemotherapy regimen. Adjuvant chemotherapy was administered to four patients (80%) with a pathological nodal status of pNx SCLC, 93 patients (74.4%) with pN0 SCLC, 41 patients (89.1%) with pN1 SCLC, and 32 patients (86.5%) with pN2-3 SCLC (S3 Table). The following reasons were provided for not administering adjuvant therapy: surgeon's or physician's decision

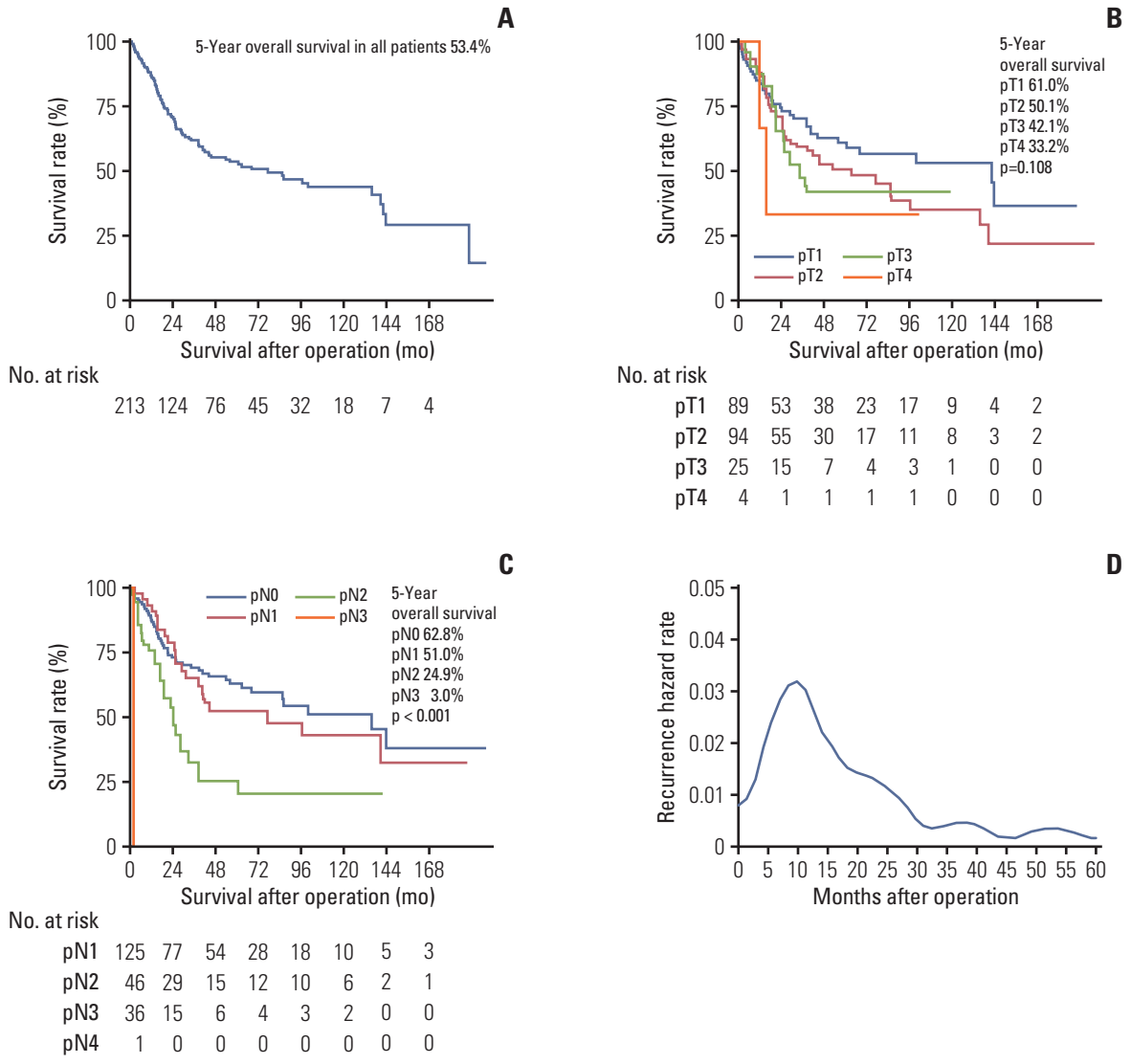

Fig. 1. Overall survival in patients underwent surgical resection. (A) Overall survival in all patients. (B) Overall survival according to the pathologic T category. (C) Overall urvival according to the pathologic N category. (D) Recurrence in all patients.

(n=11), patient refusal (n=9), poor medical condition (n=8), postoperative mortality (n=4), postoperative complications (n=3), early recurrence (n=1), and unknown (n=7).

The 5-year OS significantly improved after adjuvant chemotherapy in all patients (57.4% vs. 40.3%, p=0.007) (Fig. 2A). The survival benefit of adjuvant chemotherapy was significant in patients with negative node pathology (70.8% vs. 39.7%, p=0.004) (Fig. 2B). Adjuvant chemotherapy did not significantly improve 5-year OS in patients with positive node pathology (41.3% vs. 32%, p=0.113) (Fig. 2C). The recurrence curve for the first recurrences according to adjuvant chemotherapy status is illustrated in Fig. 2D. Patients who did not receive adjuvant chemotherapy had earlier recurrence than those who underwent adjuvant chemotherapy.

4. Role of adjuvant radiotherapy

Adjuvant radiotherapy to the mediastinum was delivered to 42 patients (19.7%). Adjuvant radiotherapy was not administered to any patient with pNx SCLC (0%), but was administered to 22 patients (17.6%) with pN0 SCLC, six patients (13%) with pN1 SCLC, and 14 patients (37.8%) with pN2-3 SCLC (p=0.004) (S4 Table).

The 5-year OS was not significantly different between patients who received adjuvant radiotherapy and those who did not (54.6% vs. 48.5%, p=0.458) (Fig. 3A). Adjuvant

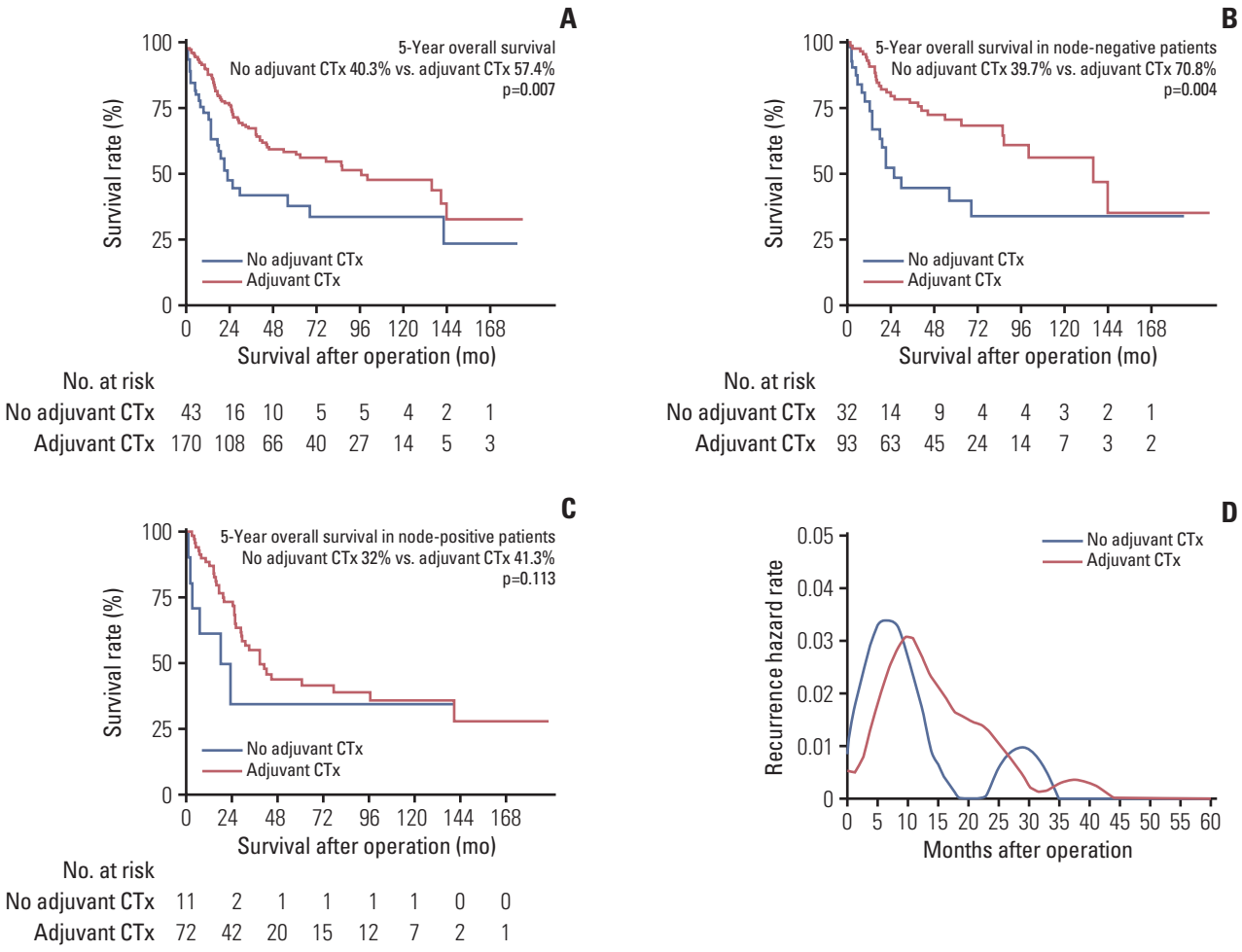

Fig. 2. Overall survival according to the adjuvant chemotherapy (CTx). (A) Overall survival according to adjuvant CTx in all patients. (B) Overall survival in patients with pathologically negative nodes according to adjuvant CTx status. (C) Overall survival in patients with pathologically positive nodes according to adjuvant CTx status. (D) Recurrence according to adjuvant CTx status.

radiotherapy was not associated with improved survival in patients with negative nodes (63.7% vs. 39.4%, p=0.759) (Fig. 3B) or in patients with positive nodes (40.2% vs. 39.4%, p=0.889) (Fig. 3C). The rate of freedom from locoregional recurrences was not significantly different between patients who received adjuvant radiotherapy and those who did not (89.9% vs. 87.2%, p=0.908) (Fig. 3D).

5. Prognostic factors for survival

Age, pN, and adjuvant chemotherapy were associated with 5-year OS according to the univariable analysis (Table 2). Age (hazard ratio [HR], 1.032; p=0.017), lymph node metastasis to the mediastinum (pN positive; HR, 2.190; p < 0.001), and adjuvant chemotherapy (HR, 0.558; p=0.019) were associated with survival after surgical resection for SCLC.

The subgroup of patients with pathologic stage I SCLC included 103 patients, of which 79 (76.7%) were administered adjuvant chemotherapy. The 5-year OS in patients with stage I SCLC who underwent adjuvant chemotherapy was 73.3% and that of patients with stage I SCLC who did not undergo adjuvant chemotherapy was 37% (p=0.001) (S2C Fig.). In this subgroup, age (HR, 1.066; p=0.011) and adjuvant therapy (HR, 0.479; p=0.040) were associated with survival (S5 Table).

Discussion

In this multi-center, retrospective study, adjuvant chemotherapy after surgical resection for SCLC improved the survival, but adjuvant radiotherapy to the mediastinum did not improve the survival or decrease the rate of locoregional recurrence. Surgical resection with adjuvant chemotherapy

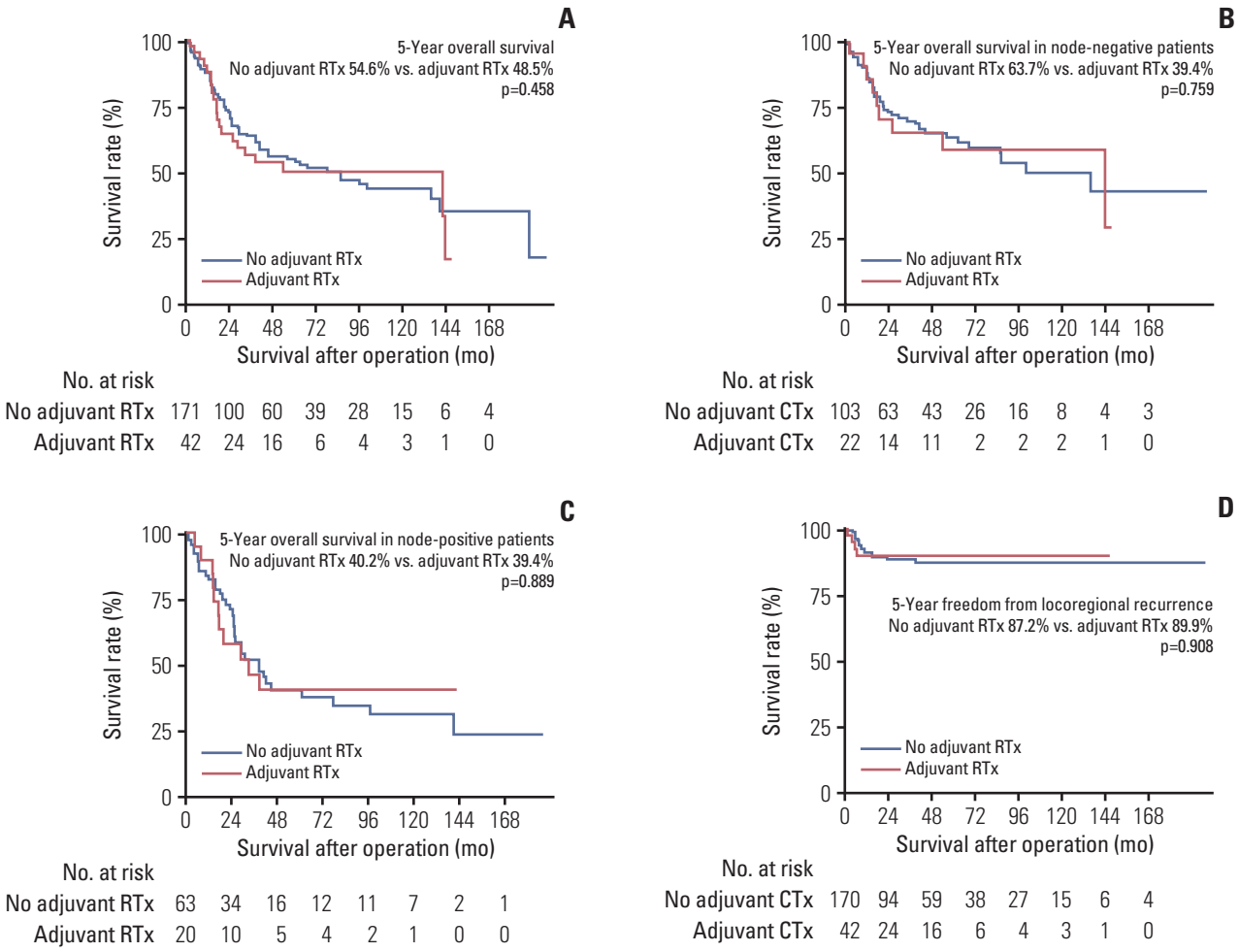

Fig. 3. Overall survival according to the adjuvant radiotherapy (RTx). (A) Overall survival of all patients according to adjuvant RTx status. (B) Overall survival in patients with pathologically negative nodes according to adjuvant RTx status. (C) Overall survival in patients with pathologically positive nodes according to adjuvant RTx status. (D) Freedom from locoregional recurrences according to adjuvant RTx status. CTx, chemotherapy.

should be considered as a treatment option for patients with SCLC.

The current National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant therapy after surgical resection for SCLC based on the pathologic nodal status [12], and recommend adjuvant radiotherapy of the mediastinum in pN+ patients, especially in pN2 patients, though this recommendation is based on limited data. The American College of Chest Physicians guidelines also recommend adjuvant chemotherapy in patients with stage I (T1-2aN0M0) SCLC who underwent surgical resection after invasive mediastinal staging and an evaluation for distant metastasis [20]. Although adjuvant chemotherapy appears to improve survival in most studies [15,17], the effects of adjuvant radiotherapy to the mediastinum on node-positive patients remain unclear [17,21]. In addition, there are few large studies that evaluate all of the adjuvant treatment modalities in patients postoperatively; therefore, this study analyzed patients who underwent surgical resection for SCLC at high-volume tertiary centers in Korea.

The results of this study indicate more favorable survival for patients with SCLC than those in previous reports. In this study, the 5-year OS was 63.8% in patients with stage I SCLC. Combs et al. [22] reported a 5-year OS of 51% for patients with stage I SCLC and 25% for patients with stage II SCLC who underwent surgery and adjuvant chemotherapy [22]. Another study reported the 5-year OS as 47% among patients with pathologic T1-2N0 tumors who underwent complete oncologic resection [15]. The results of this study emphasize the clinical importance of surgical treatment for

Table 2. Prognostic factors for overall survival in all patients

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.032 (1.007-1.057)	0.013	1.032 (1.006-1.060)	0.017
Male sex	0.883 (0.471-1.655)	0.697	-	-
Tumor size	1.053 (0.910-1.217)	0.488	-	-
pT				
T2 vs. T1	0.543 (0.130-2.266)	0.402	-	-
T3 vs. T1	0.741 (0.178-3.061)	0.678	-	-
T4 vs. T1	0.803 (0.181-3.569)	0.773	-	-
pN positive	1.795 (1.201-2.682)	0.004	2.190 (1.437-3.336)	< 0.001
Extent of operation (anatomic resection vs. sublobar resection)	0.731 (0.445-1.202)	0.217	-	-
MLND type (systematic MLND vs. others)	1.096 (0.445-2.703)	0.842	-	-
Adjuvant chemotherapy	0.545 (0.348-0.851)	0.008	0.558 (0.343-0.907)	0.019
Adjuvant radiotherapy	1.197 (0.743-1.928)	0.459	-	-
Prophylactic cranial irradiation	0.802 (0.445-1.446)	0.464	-	-

CI, confidence interval; HR, hazard ratio; MLND, mediastinal lymph node dissection.

patients with early SCLC, even when a selection bias based on the retrospective nature of this study is considered. A pneumonectomy was performed in 7% of patients in this study, and 1.8% of patients died, indicating that surgical treatment can be performed safely with careful selection of the surgical candidates. Almost all of the cases of initial recurrence were diagnosed within 1 year of surgery in this study, with a peak incidence occurring at 10 months postoperatively. The peak incidences of recurrence in patients with N1 and N2 non-SCLC have been reported as 15 months and 6 months, respectively [23,24]. Therefore, the peak incidence of recurrence in SCLC is expected to be earlier than that in non-SCLC, and it reflects the more aggressive characteristics of SCLC than non-SCLC. The recurrence hazard curve of patients with SCLC in this study did not include an obvious second peak point, indicating that careful monitoring within one year after surgical resection is needed to detect recurrences of SCLC. Distant metastases developed more frequently than locoregional recurrences, suggesting that systemic therapy may be more beneficial than other adjuvant therapies. The survival differences were not statistically significant according to the pT whereas the survival differences were prominent according to the pN; it might be related to the small numbers of patients in each pT patients and it could be interpretated that pN is more important in OS than pT.

Several previous studies have reported the survival benefits of adjuvant chemotherapy for patients with SCLC [15,17]. Yang et al. [15] reported that adjuvant chemotherapy with or without radiation was associated with significantly improved survival compared to surgery alone (HR, 0.78), which is consistent with the results of this study. Interestingly, the benefits of adjuvant chemotherapy were more prominent in pN0 patients than in pN+ patients. Though there was a tendency of improved survival in pN+ patients who received adjuvant therapy, the differences were not statistically significant. This lack of significance may be related to the small number of patients with pN+ included in this study or to the aggressiveness of node-positive SCLC. To identify patients in whom adjuvant chemotherapy may not be necessary, a subgroup analysis of patients with pStage I SCLC was conducted in this study (S3 Table). This subgroup analysis revealed that adjuvant chemotherapy was related to survival in these patients while the pT stage and tumor size were not, indicating that adjuvant chemotherapy is mandatory even in surgically-treated patients with pN0 or pStage I SCLC. However, the importance of adjuvant chemotherapy in patients with pN+ SCLC should not be overlooked and requires further investigation in larger patient populations.

Adjuvant radiotherapy was performed in a smaller proportion of patients than adjuvant chemotherapy, despite the NCCN recommendations of adjuvant radiotherapy to the mediastinum for patients with positive nodes, especially pN2 patients [12]. Previous studies have reported that < 20% of patients receive adjuvant radiotherapy [15,21]. Wakeam et al. [21] reported that adjuvant radiotherapy improves OS, and that adjuvant radiotherapy improves survival in patients undergoing sublobar resections [17]. In this study, adjuvant radiotherapy did not increase OS or reduce the locoregional recurrence rate. All patients in this study under-

went complete resection, including a complete mediastinal lymph node dissection in 93% of patients. The mean number of dissected mediastinal lymph nodes was 25.70±12.88 in this study. As adjuvant radiotherapy was effective in patients who underwent a sublobar resection group in previous studies [17,21], an anatomic resection with complete mediastinal dissection may be sufficient to control locoregional recurrence, especially in patients with early-stage SCLC. Therefore, we think that adjuvant radiotherapy, which can lead to complications, such as myocarditis, pericarditis, and esophagitis, may not be necessary in these patients. However, in patients with multi-station SCLC, bulky nodal SCLC, or extracapsular invasion of metastatic lymph nodes, adjuvant radiotherapy may help prevent locoregional recurrence. In addition, the patients who received the adjuvant CCRTx showed poor survival than the patients who received the adjuvant chemotherapy or radiotherapy only; the patients who received the adjuvant CCRTx had higher pN category (N2 33% and N1 25.6%), and advanced nodal stage might be related to the poor survival.

This study has many limitations. First, patients who received adjuvant therapy may have more favorable overall medical conditions, which may lead to a selection bias in this study. Second, the study period (17 years) is relatively long, as treatment strategies, especially adjuvant therapy and chemotherapy regimens, change over time. However, considering the small number of patients who undergo surgical resection for SCLC, this long study period is inevitable. In this study, more patients were analyzed within a shorter study period than in a previous multi-center study [18], indicating that this study population is more homogenous than that of the previous study. The four institutions included in this study have similar surgical strategies regarding mediastinal lymph node dissection, though the policies do vary slightly. Third, patients with clinically-positive nodes were included in this study, though most of these patients were not preoperatively diagnosed with SCLC or other pathology (no patients were diagnosed with SCLC preoperatively). These patients should be included in the analysis as there are several surgical cases based only on radiologic findings without exact pathology in clinical practice. In addition, as a retrospective study, there were no consistent indications for surgery and adjuvant therapy and for SCLC among the four institutions. The chemotherapy and radiotherapy regimens were not also consistent between the institutions during the study periods. Despite these limitations, this multi-center study provides a meaningful analysis of a relatively homogenous patient population with detailed information.

In conclusion, adjuvant chemotherapy after surgical resection for SCLC improved OS, though adjuvant radiotherapy to the mediastinum did not improve OS or decrease the locoregional recurrence rate. As this is a retrospective study, these findings should be evaluated further in randomized controlled trials.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

The study was approved by the appropriate institutional review boards (Asan Medical Center 2021-1118, Samsung Medical Center 2021-07-059, Seoul National University Hospital 2106-146-1230, Yonsei University Severance Hospital; 4-2021-0619), and the requirement of patient consent was waived under the approval of IRB as a retrospective study.

Author Contributions

Conceived and designed the analysis: Park SY, Park S, Lee GD, Kim HK, Cho JH.
Collected the data: Choi S, Kim HR, Kim YH, Kim DK, Park SI, Hong TH, Choi YS, Kim J, Shim YM, Zo JI, Na KJ, Park IK, Kang CH, Kim YT, Park BJ, Lee CY, Lee JG, Kim DJ, Paik HC.
Contributed data or analysis tools: Choi S, Kim HR, Kim YH, Kim DK, Park SI, Hong TH, Choi YS, Kim J, Shim YM, Zo JI, Na KJ, Park IK, Kang CH, Kim YT, Park BJ, Lee CY, Lee JG, Kim DJ, Paik HC.
Performed the analysis: Park SY, Park S.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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