Original Article

Adjuvant treatment for patients with incidentally resected limited disease small cell lung cancer—a retrospective study

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Background: With the exception of very early-stage small cell lung cancer (SCLC), surgery is not typically recommended for this disease; however, incidental resection still occurs. After incidental resection, adjuvant salvage therapy is widely offered, but the evidence supporting its use is limited. This study aimed to explore proper adjuvant therapy for these incidentally resected SCLC cases.

Methods: Patients incidentally diagnosed with SCLC after surgery at the Shanghai Pulmonary Hospital in China from January 2005 to December 2014 were included in this study. The primary outcome was overall survival. Patients were classified into different group according to the type of adjuvant therapy they received and stratified by their pathological lymph node status. Patients' survival was analyzed using a Kaplan-Meier analysis and Cox regression analysis.

Results: A total of 161 patients were included in this study. Overall 5-year survival rate was 36.5%. For pathological N0 (pN0) cases (n=70), multivariable analysis revealed that adjuvant chemotherapy (ad-chemo) was associated with reduced risk of death [hazard ratio (HR): 0.373; 95% confidence interval (CI): 0.141–0.985, P=0.047] compared to omission of adjuvant therapy. For pathological N1 or N2 (pN1/2) cases (n=91), taking no adjuvant therapy cases as a reference, the multivariable analysis showed that ad-chemo was not associated with a lower risk of death (HR: 0.869; 95% CI: 0.459–1.645, P=0.666), while adjuvant chemo-radiotherapy (ad-CRT) was associated with a lower risk of death (HR: 0.279; 95% CI: 0.102–0.761, P=0.013).

Conclusions: Patients who incidentally receive surgical resection and are diagnosed with limited disease SCLC after resection should be offered adjuvant therapy as a salvage treatment. For incidentally resected pN0 cases, ad-chemo should be considered and for pN1/2 cases, ad-CRT should be received.

Keywords: Small cell lung cancer (SCLC); surgery; adjuvant therapy

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Introduction

Historically, small cell lung cancer (SCLC) has been considered a non-operable disease. Two completed prospective randomized control trials (1,2) suggested that surgery had no benefits compared to radiation in the treatment of limited-stage SCLC. Over the past 20 years, several retrospective single-institution (3-7) or database-based studies (8-15) have reported favorable results for surgical resection in patients with early-stage SCLC. Under the current National Comprehensive Cancer Network (NCCN) guidelines (16), American College of Chest Physician (ACCP) guidelines (17), and European Society for Medical Oncology (ESMO) guidelines (18), surgery with adjuvant therapy is now recommended for the treatment of patients with clinical T1–2N0M0 or stage I SCLC.

It is currently recommended that only T1–2N0M0 or stage I SCLC cases receive surgical resection (16-18); however, a considerable number of patients with N1 or N2 lymph node metastatic SCLC ultimately undergo surgical resection in clinical practice. This may partially attributed to some patients receiving an incidental diagnosis after resection for what was initially presumed to be non-small cell lung cancer (NSCLC), pulmonary metastatic disease, or other diseases when the decision for surgical resection is made (6,11). This problem is not new; already three decades ago, incidental SCLC findings occurred in 4–12% of surgeries for solitary lung nodules (19).

Surgery without chemotherapy has been shown to provide no benefit to patients with SCLC (1). Thus, adjuvant therapy, as a salvage treatment, might improve the survival of patients with incidentally resected SCLC. However, the proper adjuvant therapy for SCLC patients who undergo resections (both purposely and incidentally) is still unclear.

According to ESMO guidelines, adjuvant chemotherapy (ad-chemo) is recommended for pT1–2N1 patients who receive complete surgical resection (R0), while adjuvant chemo-radiotherapy (ad-CRT) is recommended for N2 patients (18). According to NCCN guidelines, ad-CRT is recommended for both N1 and N2 patients, though data to support this recommendation are sparse (16). In sum, the use of proper adjuvant therapy for N1–2 cases remains controversial and needs further study.

NCCN (16) and ACCP guidelines (17) would suggest that ad-chemo is recommended for patients with T1–2N0 (stage I) resected SCLC. Due to the relative infrequency of such surgical candidates, this recommendation is only supported by 4 quite dated phase-II single-arm studies (20-23) and a database-based retrospective study (24). It is clear that further research needs to be conducted on the use of adjuvant therapy for patients with incidentally resected N1-2 SCLC. In addition, further research also needs to be conducted on the use of adjuvant therapy for patients with incidentally resected N0 cases because the evidence is limited.

This study aimed to evaluate outcomes of patients with incidentally resected SCLC to explore the use of salvage adjuvant therapy, stratified by absence (pN0) or presence (pN1-2) of pathologic lymph node metastasis. We hypothesized that ad-chemo and/or ad-CRT could improve survival of patients after incidentally resected. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-616/rc).

Methods

Patient selection

Consecutive patients who underwent surgical resection and were diagnosed with SCLC after resection from January 2005 to December 2014 at the Shanghai Pulmonary Hospital were retrospectively included in this study. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had been treated with palliative intent; (II) had positive surgical margin; (III) had been diagnosed with other malignant tumors; (IV) died within 30 days after surgery; and/or (V) were lost to follow-up during the designated period. The number of cases in the area during the study period determined the sample size. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Shanghai Pulmonary Hospital (No. K20-196Y), and individual consent for this retrospective analysis was waived.

Diagnosis and treatment

The preoperative workup for lung resection patients at this institution routinely included chest computed tomography (CT), brain magnetic resonance imaging, a whole-body bone scan, an ultrasound or CT scan of the abdomen, and fiberoptic or electronic bronchoscopy. Positron emission tomography/CT was not mandatory for all patients. All patients received an exfoliative cell examination of

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sputum and a bronchoscopic brush biopsy. Endobronchial ultrasound-guided transbronchial needle aspiration was performed in patients with enlarged mediastinal lymph nodes. Patients with peripheral nodules also underwent transthoracic needle biopsy.

Patients without a definite SCLC diagnosis, but in whom lung cancer was highly suspected, underwent surgical resection based on treatment principles for NSCLC. All patients underwent surgery without induction chemotherapy. After resection, it was recommended that all patients receive 4–6 courses of adjuvant platinum-based chemotherapy. For patients with malignant lymph nodes, ad-CRT was an alternative option. Some patients also received prophylactic cranial irradiation (PCI). All adjuvant therapy was performed before tumor recurrence. Tumor, node, metastasis (TNM) staging was determined according to the 7th edition of the TNM classification system for lung cancer (25). The pathologic diagnoses were confirmed by 2 senior pathologists.

Patients were stratified into pN0 or pN1–2 groups according to their pathological lymph nodes status and further grouped according to different adjuvant therapies (surgery alone, ad-chemo, ad-CRT, ad-chemo + PCI and ad-CRT + PCI). For pN0 cases, survival were compared between surgery alone and ad-chemo groups and for pN1/2 cases, survival were compared among surgery alone, ad-chemo and ad-CRT groups, because the number of patients in some adjuvant therapies were too small.

Outcome

The primary outcome was overall survival (OS). OS was defined as the time from receiving surgery to death or the last follow-up time-point. Survival was updated by telephone contact annually. Patients who were not deceased were censored at the date they were last known to be alive. Patients' outcomes were recorded up to December 31, 2020.

Statistical analysis

Continuous variables were compared using the Student's *t*-test. Unordered categorical variables were analyzed using Pearson's chi square test or the Fisher exact test, and ordered categorical variables were analyzed using the Mann-Whitney test. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Multivariable cox regression models using a stepwise backwards (Wald) method were constructed to identify the relevant variables affecting survival. Independent variables included age, gender, symptoms, comorbidities, ward characteristics, laterality, surgical approaches, surgical methods, surgical margins, postoperative complications, histologic types, pT category, pN category, and types of adjuvant therapy. Only factors that were significantly associated with a specific outcome in univariate analysis ($P<0.05$) were included in the multivariate analysis. A 2-sided P value <0.05 was considered statistically significant. The statistical analysis was performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA), and the survival curves were drawn using GraphPad Prism 6.0 (GraphPad Software, San Diego, CA, USA).

Results

Therapy information and baseline characteristics

Between 2005 and 2014, 15,368 patients who underwent surgical resection were diagnosed with primary lung cancer at the Shanghai Pulmonary Hospital in China. A total of 290 (1.9%) of these patients were diagnosed with SCLC, and 193 (1.3%) patients were diagnosed incidentally after resection. One hundred and sixty one patients met the eligibility criteria and were included in this study (see *Figure 1*). Among these 161 incidental cases, 103 (64.0%) patients received ad-chemo, 13 (8.1%) received ad-CRT, 9 (5.6%) received ad-chemo and PCI, and 1 (0.6%) received ad-CRT and PCI, while the remaining 35 (21.7%) received surgery alone. The baseline characteristics of the patient cohort are listed in *Table 1*. There were no missing values for all the relevant variables. Of the patients who received adjuvant therapy, a higher proportion had symptoms before diagnosis, compared to patients who received no adjuvant therapy (63.3% *vs.* 81.8%, P=0.041).

OS for the entire cohort

The median follow-up time was 33.6 months (interquartile range, 15.7–67.4 months). The median OS of the entire cohort was 36.6 months (95% CI: 28.5–44.8 months), and the 5-year OS rate was 36.5%. Median survival times (MST) and 5-year OS rates for the pathologic stage I, II, and III patients were "not reached" and 53.6%, 39.1 months and 40.8%, 20.7 months and 22.2%, respectively (log-rank P<0.001).

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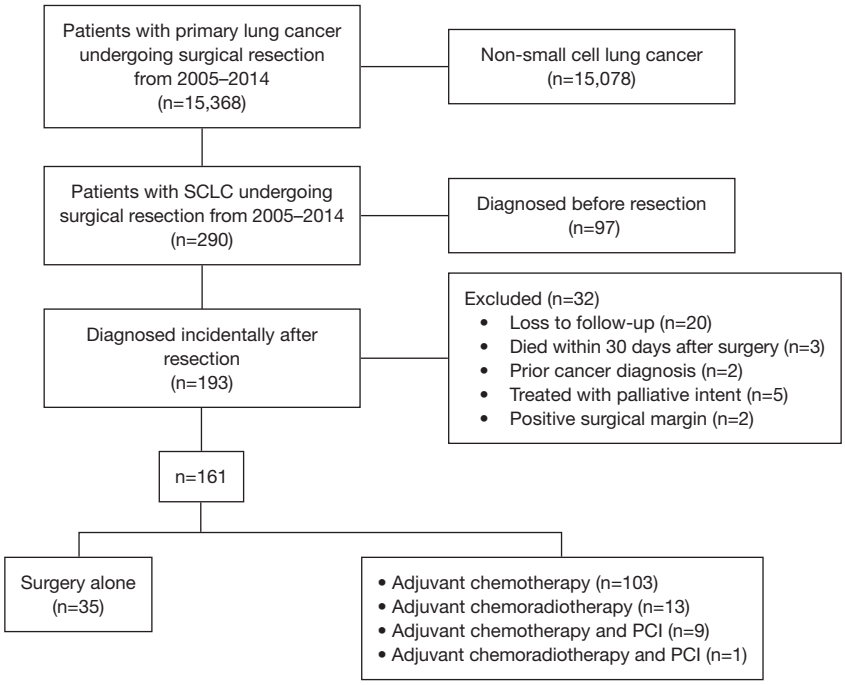

Figure 1 CONSORT diagram showing schema of study patient selection. SCLC, small cell lung cancer; PCI, prophylactic cranial irradiation.

Table 1 Baseline characteristics for patients with incidentally resected SCLC

Characteristic	Patient cohort (N=161)	Adjuvant therapy (n=126)	No adjuvant therapy (n=35)	P
Age (years)[a]				0.332
Mean ± SD	61.1±9.6	60.6±9.2	63.0±10.7	
Median (Q1, Q3)	61.0 (55.0, 68.0)	61.0 (55.0, 67.0)	64.0 (56.0, 72.0)	
Gender, n (%)				0.970
Male	140 (87.0)	109 (88.6)	31 (88.6)	
Female	21 (13.0)	17 (13.4)	4 (11.4)	
Laterality, n (%)				0.347
Left	85 (52.8)	64 (50.8)	21 (60.0)	
Right	76 (47.2)	62 (49.2)	14 (40.0)	
Symptoms, n (%)				0.041
Without	53 (32.9)	47 (36.7)	6 (18.2)	
With	108 (67.1)	81 (63.3)	27 (81.8)	
Comorbidities, n (%)				0.222
Without	108 (67.1)	81 (64.3)	27 (77.1)	
With	53 (32.9)	45 (35.7)	8 (22.9)	
Ward character, n (%)				1.000
General ward	137 (85.1)	107 (84.9)	30 (85.7)	

Table 1 *(continued)*

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Table 1 *(continued)*

Characteristic	Patient cohort (N=161)	Adjuvant therapy (n=126)	No adjuvant therapy (n=35)	P
Priority ward	24 (14.9)	19 (15.1)	5 (14.3)	
FEV1%, mean ± SD	85.8±16.5	81.2±14.8	87.0±16.8	0.169
Year of diagnosis, n (%)				0.546
2005–2009	55 (34.2)	45 (35.7)	10 (28.6)	
2010–2014	106 (65.8)	81 (64.3)	25 (71.4)	
Surgical approach, n (%)				0.864[a]
Open	120 (74.5)	94 (74.6)	26 (74.3)	
VATS	40 (24.8)	31 (24.6)	9 (25.7)	
VATS converted to open	1 (0.4)	1 (0.8)	0 (0)	
Surgical method, n (%)				0.513
Sub-lobectomy	10 (6.2)	7 (5.6)	3 (8.6)	
Lobectomy	118 (73.3)	91 (72.2)	27 (77.1)	
Pneumonectomy	33 (20.5)	28 (22.2)	5 (14.3)	
Surgical margin, n (%)				0.786
>2 cm	138 (85.7)	107 (88.6)	31 (88.6)	
≤2 cm	23 (14.3)	19 (15.1)	4 (11.4)	
Complications, n (%)				0.059
Without	137 (85.1)	111 (88.1)	26 (74.3)	
With	24 (14.9)	15 (11.9)	9 (25.7)	
Pathologic T category, n (%)				0.060
T1	60 (37.3)	43 (34.1)	17 (48.6)	
T2	67 (41.6)	57 (45.2)	10 (28.6)	
T3	25 (15.5)	17 (13.5)	8 (22.9)	
T4	9 (5.6)	9 (7.1)	0 (0.0)	
Pathologic N category, n (%)				0.343
N0	70 (43.5)	51 (40.5)	19 (54.3)	
N1	24 (14.9)	20 (15.9)	4 (11.4)	
N2	67 (41.6)	55 (43.7)	12 (34.3)	
Histologic types, n (%)				0.127
SCLC	77 (47.8)	56 (44.4)	21 (60.0)	
Combined SCLC	84 (52.2)	70 (55.6)	14 (40.0)	
Length of postoperative stay, n (%)				0.664
<14 days	120 (74.5)	95 (75.4)	25 (71.4)	
≥14 days	41 (25.5)	31 (24.6)	10 (28.6)	

[a], 1 patient who underwent VATS but converted to open surgery was not included in the model when testing. SCLC, small cell lung cancer; FEV1, forced expiratory volume in 1 s; VATS, video-assistant thoracoscopic surgery.

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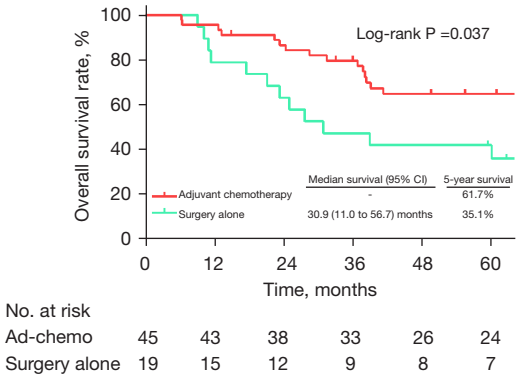

Figure 2 OS for patients with incidentally resected pN0 SCLC who underwent surgery alone or ad-chemo. OS, overall survival; SCLC, small cell lung cancer.

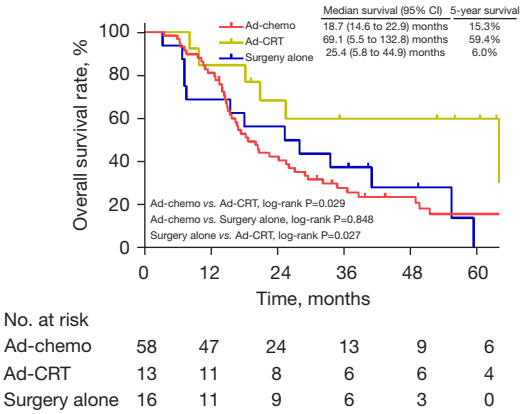

Figure 3 OS for patients with incidentally resected pN1/2 SCLC who underwent surgery alone, ad-chemo, or ad-CRT. OS, overall survival; SCLC, small cell lung cancer; CRT, chemo-radiotherapy.

Table 2 Factors independently associated with OS for patients with incidentally resected pN0 SCLC who underwent surgery alone or surgery + ad-chemo in the multivariable Cox analysis

Variable	Hazard ratio	95% CI	P
Age ≥60 years	3.456	1.069–11.172	0.038
Postoperative complications	3.074	0.952–9.928	0.060
Comorbidities	2.874	1.029–8.025	0.044
Surgical methods			
Pneumonectomy *vs.* lobectomy	15.569	3.763–64.415	<0.001
Sub-lobectomy *vs.* lobectomy	4.604	1.568–13.521	0.005
Surgical margin ≤2 cm	4.911	1.348–17.883	0.016
Ad-chemo *vs.* surgery alone	0.373	0.141–0.985	0.047

OS, overall survival; SCLC, small cell lung cancer; CI, confidence interval.

Comparison of different types of adjuvant therapy in pN0 cases

Of the 70 patients with pN0 SCLC who were diagnosed incidentally, 45 (64.3%) received ad-chemo, 19 (27.1%) received surgery alone, and the remaining 6 (8.6%) patients received ad-chemo + PCI. The Kaplan-Meier analysis demonstrated that ad-chemo was associated with better OS than surgery alone [median OS: not reached *vs.* 30.9 (95% CI: 11.0–56.7) months; 5-year OS rates: 61.7% *vs.* 35.1%; log-rank P=0.037; see *Figure 2*]. After adjusting for age, postoperative complications, comorbidities, surgical methods and surgical margin, multivariable Cox regression showed that ad-chemo was associated with a lower risk of death than surgery alone (HR: 0.373, 95% CI: 0.141 to 0.985; see *Table 2*).

Comparison of different types of adjuvant therapy in pN1–2 cases

Of the 91 patients with pathologic positive lymph nodes (pN1–2) who were diagnosed incidentally, 58 (63.7%) received ad-chemo, 13 (14.3%) received ad-CRT, 16 (17.6%) patients received surgery alone, and the other 4 (4.4%) patients received some other types of adjuvant therapy (3 received ad-chemo + PCI and 1 received ad-CRT + PCI). When comparing survival among the patients who received ad-chemo, ad-CRT, and surgery alone, the Kaplan-Meier analysis showed that ad-CRT was associated with the longest survival [median OS: 69.1 (95% CI: 5.5–132.8) months; 5-year OS: 59.4%; see *Figure 3*]. Ad-chemo was not associated with better survival than surgery alone [median OS: 18.7 (95% CI: 14.6–22.9) *vs.* 25.4 (95% CI: 5.8–44.9) months; 5-year OS: 15.3% *vs.* 6.0%; log-rank P=0.848]. After adjusting for surgical margin, symptoms, ward character and laterality, multivariable Cox regression analysis showed that ad-CRT was associated with a lower risk of death (HR: 0.279, 95% CI: 0.102–0.761), while ad-chemo was not (HR: 0.869, 95% CI: 0.459–1.645) compared to surgery alone (see *Table 3*).

Discussion

In this single-institution retrospective study, we evaluated

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Table 3 Factors independently associated with OS for patients with incidentally resected pN1/2 SCLC who underwent surgery alone, surgery + ad-CRT or surgery + ad-CRT in the multivariable Cox analysis

Variable	Hazard ratio	95% CI	P
Surgical margin ≤2 cm	2.707	1.148–6.385	0.023
Symptoms	1.715	1.008–3.042	0.047
Adjuvant therapy (ref. = surgery alone)			
Ad-chemo	0.869	0.459–1.645	0.666
Ad-CRT	0.279	0.102–0.761	0.013
Priority ward *vs.* common ward	0.293	0.105–0.822	0.020
Laterality (left *vs.* right)	0.539	0.318–0.913	0.022

OS, overall survival; SCLC, small cell lung cancer; CRT, chemo-radiotherapy; CI, confidence interval.

the role of adjuvant therapy in patients with SCLC who incidentally received complete surgical resection. For pN0 patients, ad-chemo was associated with significantly better OS than surgery alone. For pN1-2 patients, ad-CRT was associated with longer OS than surgery alone or ad-chemo, while ad-chemo was not associated with better OS than surgery alone.

Only about 5% of SCLC cases are considered surgically resectable (26), and due to the rarity of resectable SCLC cases, no prospective studies have been conducted comparing surgery alone, ad-chemo, and ad-CRT in patients with SCLC. Recently, 2 studies (24,27) evaluated the optimal adjuvant therapy for pT1–2N0 and N1-2 cases, respectively.

Based on the National Cancer Data Base (NCDB), Yang *et al.* (24) performed the only study to evaluate the role of adjuvant therapy in patients with pT1–2N0M0 SCLC who underwent resection, and found that ad-chemo was associated with better survival than surgery alone (MST 59.8 *vs.* 42.1; 5-year OS: 50.0% *vs.* 40.4%). Their results provided support for the current NCCN guidelines that also recommend ad-chemo after resection for T1–2N0M0 SCLC patients (16). However, Yang's study (24) was limited in terms of information regarding surgical complications and recurrence, which made identifying adjuvant treatment indistinguishable from palliative treatment and severely impacted any interpretation of results (28). The current study had the advantage of including such information beyond what was presented by in Yang *et al.* In our study, patients with resected pN0 patients were found to benefit from ad-chemo after resection, and had a 63.2% 5-year survival rate. The multivariate Cox model showed that ad-chemo was an independent prognostic factor for pN0 patients who received resection. Our single-institution result, with surgical complications, pulmonary functions and recurrence information, verified and corroborates the conclusions illustrated by Yang *et al.* (24).

Urushiyama *et al.* (27) compared ad-chemo and ad-CRT in patients with resected N1–2 SCLC in a retrospective study using the Diagnosis Procedure Combination (DPC) database in Japan. Median recurrence-free survival (RFS) was 1,146 days in the ad-chemo group and 873 days in the ad-CRT group. RFS was significantly longer in ad-chemo patients than ad-CRT patients in the univariable analysis. However, in the multivariable analysis, RFS did not differ significantly between the ad-CRT and ad-chemo groups (HR: 1.29; 95% CI: 0.91–1.84). In Urushiyama's study (27), recurrence could not be recorded if patients were discharged to another hospital or home before recurrence, limiting the validity of results. As deaths in hospitals other than those participating in the DPC database could not be recorded, findings on OS were not available in Urushiyama's study.

An additional study utilizing the NCDB by Wong *et al.* (29) reported that postoperative radiotherapy (PORT) significantly improved the 5-year OS rates of patients with pathologic N2 SCLC from 18.6% to 29.0% but did not improve the survival of patients with pathologic N1 SCLC. In this study (29), 44.9% of patients did not receive chemotherapy in the no-PORT group, while only 3.8% of patients did not receive chemotherapy in the PORT group; the poor survival of the no-PORT group might be explained by the higher rate of patients who did not receive chemotherapy. The advantage of PORT in N2 disease retained its significance in the multivariate analysis; however, a formal comparison of surgery alone, ad-chemo, and ad-CRT might still be necessary.

To our knowledge, this is the first study to compare surgery alone, ad-chemo, and ad-CRT for patients with incidentally resected pN1–2 SCLC. We found that ad-CRT significantly improved OS compared to surgery alone or ad-chemo. Our findings support the recommendation in the NCCN guidelines to use adjuvant treatment in patients with pathologic positive lymph nodes. In addition, we found that ad-chemo did not improve OS compared to surgery alone for incidentally resected pN1–2 SCLC cases, which is the first time such a finding has been reported.

This study had several limitations. First, this study carries the inherent bias of a retrospective randomized study, and our conclusions would ideally be further verified

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in a prospective manner. It was recommended that all patients received ad-chemo, but some patients refused to receive adjuvant therapy, which may have impacted those patients' outcome. The baseline characteristics between the patients who received adjuvant therapy and those who did not were compared, and only a proportion of patients with symptoms differed significantly between the two groups (see *Table 1*). Patients with symptoms or who are less fit might be less likely to receive aggressive therapy. For pN0 cases, we compare ad-chemo to surgery alone, but no patients received ad-CRT, so we cannot provide new data about tri-modality therapy among these patients. For pN1/2 cases, ad-CRT was an alternative option to ad-chemo, and we do not know the exact reasons why patients chose to receive ad-CRT and not ad-chemo. The possible reason might be physicians recommended one over the other, but we had no data to prove it. Second, our analysis was limited by the sample size. Patients with pN1 or pN2 SCLC were analyzed together, not separately, because of the limitation of the small sample size. Even the multivariate analysis for patients with pN1/2 SCLC did not reveal that pN2 was associated with a higher risk of death than pN1; thus, a separate analysis of pN1 or pN2 cases needs to be conducted in the future. Third, only 10 patients (6 with pN0 SCLC and 4 with pN1–2 SCLC) received PCI after resection. These 10 patients were not included in the survival analysis because of the limitation of the small sample size. PCI may provide a benefit to patients with stage IIB or III SCLC who have received complete resection (30,31), and optimal adjuvant therapy for pN1–2 incidentally resected patients might include PCI. Despite these limitations, which we acknowledge, this study closes a knowledge gap regarding the benefits of salvage adjuvant therapy following incidental resection of SCLC, with important clarifying results as stratified by nodal status. We have set the foundation for future prospective evaluations.

Conclusions

Patients who incidentally receive surgical resection and are diagnosed with limited disease SCLC after resection should be offered adjuvant therapy as a salvage treatment. For patients with incidentally resected pN0 SCLC, ad-chemo should be considered after resection. For patients with incidentally resected pN1/2 SCLC, ad-chemo does not improve OS compared to surgery alone in our cohort, and these patients should receive ad-CRT as an adjuvant therapy.

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Footnote

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Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-616/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by

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the Institutional Review Board of Shanghai Pulmonary Hospital (No. K20-196Y), and individual consent for this retrospective analysis was waived.

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