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ORIGINAL ARTICLE

# Analysis of long-term outcomes and application of the tumor regression grading system in the therapeutic assessment of resectable limited-disease small cell lung cancer

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## Abstract

**Objective** The present study attempted to evaluate the value of neoadjuvant chemotherapy in limited-disease small cell lung cancer (LD-SCLC), and to identify the predictive value of the tumor regression grading (TRG) system in LD-SCLC treatment-response and prognosis.

**Methods** The records of patients with LD-SCLC (p-Stage I–IIIa) who underwent definitive radical resection at Shaanxi Provincial People's Hospital between March 1, 2000 and March 31, 2014 were retrospectively analyzed. We compared the disease-free survival (DFS) and overall survival (OS) rates between Group A patients (patients who underwent surgery combined with pre- and post-operative chemotherapy) and Group B patients (patients who underwent surgery combined with adjuvant chemotherapy only) using the Kaplan-Meier method and the Mantel-Cox test. The specimens of patients who received neoadjuvant chemotherapy were reassessed according to the TRG system.

**Results** The median DFS for 27 patients was 16.267 months and the median OS was 81.167 months (1-year OS, 74.07%; 3-year OS, 22.22%; 5-year OS, 14.81%). Thirteen patients received neoadjuvant chemotherapy, and their specimens were reassessed by TRG (pathological complete remission, 3/13, 23.08%). Patients in group A had a longer OS than those in group B (mean, 93.782 months versus 42.322 months, $P = 0.025$), although there was no significant difference in DFS between the two groups (median 20.100 months versus 14.667 months, $P = 0.551$). Statistical analysis revealed that TRG Grade (G) 0 (mean, 61.222 months) was associated with better OS than G1-2 (mean, 31.213 months) ($P = 0.311$).

**Conclusion** Our study indicated that neoadjuvant chemotherapy combined with surgical resection may represent a feasible treatment method for patients with LD-SCLC. The TRG system may be a valuable prediction tool to assess neoadjuvant chemotherapeutic efficacy, especially in patients with G0 disease as determined by TRG; these patients may attain an improved survival benefit with neoadjuvant chemotherapy.

**Key words:** small cell lung cancer; tumor regression grading; neoadjuvant chemotherapy

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Radical surgical resection is the recommended treatment for patients with early-stage (limited-stage, lymphadenopathy-negative) small cell lung cancer (SCLC), according to the latest National Comprehensive Cancer Network (NCCN) guidelines [1]. SCLC is characterized by a number of malignant biological features, such as rapid proliferation, early metastases, and frequent relapse; as a result, the majority of SCLC patients have dismal long-term survival outcomes [2]. Patients suitable for resection represent < 5% of all SCLC patients [3]. It has been determined that multimodality treatment methods, combining surgery with chemoradiotherapy, provide patients with

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more survival benefits. In a study of 41 patients with limited-disease (LD)-SCLC, Chen *et al* [4] reported that for patients with p-Stage IIIa (N2-positive), the 5-year overall survival (OS) rate in patients who underwent both pre- and post-operative chemotherapy was significantly better than that in patients who received only postoperative chemotherapy (34% versus 12%, $P = 0.020$). A multicenter clinical trial (JCOG9101) [5] showed that 61 patients with stage I–IIIa SCLC who received adjuvant chemotherapy, consisting of four cycles of cisplatin and etoposide, followed by surgical resection yielded a 3-year OS rate of 61%. However, an essential role for preoperative adjuvant chemotherapy in LD-SCLC treatment has not yet been established.

The Response Evaluation Criteria In Solid Tumor (RECIST) guidelines are routinely used to evaluate the efficacy of chemotherapy in lung cancer [6–7]. Given that surgical resection is infrequently performed in patients with LD-SCLC, there is a strong demand for tools that will inform the choice of therapy. The tumor regression grading (TRG) system has been used to evaluate the efficacy of treatment in digestive tract tumors [8–10], but to our knowledge, it has been rarely used to assess response to neoadjuvant chemotherapy in patients with SCLC. In this study, we analyzed the clinical outcomes of patients with SCLC and evaluated the prognostic ability of the TRG system in these patients. Furthermore, we evaluated the association between response to preoperative chemotherapy and postoperative survival.

## Patients and methods

### Criteria

We retrospectively evaluated the cases of 37 patients with SCLC who underwent radical surgical resections in Shaanxi Provincial People's Hospital between March 1, 2000 and March 31, 2014. The selection criteria were as follows:

(1) Patients were diagnosed with LD-SCLC on routine workup. Tumor location was limited to one hemithorax; local involvement of the supraclavicular, hilar, or mediastinal lymph nodes was acceptable (ipsilateral and/or contralateral). Diagnosis and location was confirmed through evaluation of bronchoscopic biopsies and surgical specimens; clinical stage did not progress beyond IIIa.

(2) Complete preoperative evaluations were performed; this included brain magnetic resonance imaging (MRI)/computed tomography (CT), chest CT, upper abdominal ultrasonography/CT, bronchoscopy, and whole-body bone scintigraphy. These evaluations confirmed that there was no distant metastasis. Of note, one male patient did not undergo the above-mentioned workup. However, he underwent positron emission tomography, and was therefore included.

(3) All patients received adjuvant therapy.

(4) All surgical resections were R0 resections.

(5) Patients were not diagnosed with second primary tumors or serious cardiac or pulmonary disease.

(6) Patients did not die during the perioperative period (survived for > 3 months).

Pathological diagnosis, preoperative clinical stage, and postoperative pathological stage were defined based on the WHO classification of tumors and the Tumor, Node, Metastasis (TNM) staging system (7th edition) [11]. Ten patients were excluded because their postoperative follow-up was too short (< 3 weeks after surgery) or their treatment involved resection only. Finally, 27 patients were enrolled in our study group.

### Neoadjuvant chemotherapy

In accordance with SCLC management guidelines and the Eastern Cooperative Oncology Group guidelines [12–13], neoadjuvant chemotherapy was administered to patients with a performance status (PS) < 2 (0 or 1), following an accurate pathological diagnosis of SCLC. Neoadjuvant treatment included a platinum-based regimen (100 mg/m$^2$ cisplatin or 400 mg/m$^2$ carboplatin on Day 1 for at least two cycles at 3-weeks intervals). After neoadjuvant therapy, resection was performed.

### TRG

In accordance with the histological TRG criteria and NCCN guidelines for gastroesophageal carcinoma [8–10], the extent of any residual cancer was evaluated under the microscope. To ensure accuracy, two pathologists were invited to double-check the results. No residual cancer was defined as TRG Grade (G) 0, < 50% residual cancer was defined as G1, and > 50% residual cancer was defined as G2 [9].

### Postoperative treatments

During the postoperative period, all patients underwent adjuvant chemotherapy. Neoadjuvant and adjuvant chemotherapy were administered to 13 patients. Adjuvant chemotherapy alone was administered to 14 patients. Prophylactic cranial irradiation (PCI) and irradiation of the region of recurrence was performed in five and eight patients, respectively. Adjuvant platinum-based therapy was continued unless serious hematologic toxicity or death occurred; however, some patients refused to accept further treatment. Similar to the neoadjuvant treatment format, the adjuvant chemotherapy was administered to patients with PS < 2 and consisted of 80 mg/m$^2$ etoposide on Days 1–3 plus cisplatin/carboplatin, for two to six cycles at 3-week intervals. The radiotherapy dosage was 1.5–2.0 Gy per fraction, to a total dose of 24–40 Gy.

### Follow-up

Follow-up information included outpatient clinic visits and phone and mail correspondence. Brain CT/MRI, chest CT, upper abdominal ultrasonography, and whole-body bone scintigraphy were assessed. The tracking intervals were every 6 months for first 2 postoperative years, followed by once a year thereafter. The follow-up end-point was defined as the date of recurrence or death, or the date of last follow-up. All records were updated before May 31, 2014.

### Statistical analysis

Pearson's *chi-square* test was used to compare the differences across categorical variables. Kaplan-Meier curves and the Mantel-Cox test were used to calculate and evaluate disease-free survival (DFS) and OS, respectively. Tests were two-sided. A $P$ value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 16.0.

## Results

### General information

Our study cohort consisted of 22 males (81.48%) and 5 females (18.52%) patients with SCLC who underwent radical surgical resections. The mean patient age was 56.59 years (range, 37.00–77.00 years). Based on the postoperative pathological examinations, solid tumors were confirmed in all 27 cases: 21 cases of single small-cell carcinoma and 3 cases of mixed carcinoma (small-cell carcinoma and squamous carcinoma); in 3 cases, cancer cells were not found in the remainder of the removed lung tissues. The specific characteristics are listed in Table 1. Group A represented patients who received neoadjuvant chemotherapy, and Group B represented patients who did not receive neoadjuvant chemotherapy.

### Survival analysis

The median postoperative follow-up time for the 27 patients in our study was 20.50 months. Fig. 1 show that the median DFS was 16.267 months, and the median OS was 81.167 months, with overall 1-, 3- and 5-year survival rates of 74.07%, 22.22%, and 14.81%, respectively. Subgroup evaluation was performed using univariate analysis. Comparing group A with group B, the former had better postoperative survival outcomes: mean DFS, 20.100 months versus 14.667 months, $P$ = 0.551; mean OS, 93.782 months versus 42.322 months, $P$ = 0.025 (Fig. 2–3). Moreover, we confirmed that the pathological lymph node stage influenced DFS in our study. Patients diagnosed with pN0-1 disease attained more survival benefit than those diagnosed with pN2, especially in terms of DFS ($P$ = 0.036) (Table 2).

Table 1 Patient characteristics ($n$ = 27)

| Variate | Group A | | Group B | | P value |
|---|---|---|---|---|---|
| | *n* | % | *n* | % | |
| Numbers of cases | 13 | | 14 | | |
| Age (years) | 52.7 | | 60.4 | | 0.017 |
| ≥ 65 | 0 | 0 | 5 | 35.7 | |
| < 65 | 13 | 100 | 9 | 64.3 | |
| Gender | | | | | 0.557 |
| Male | 10 | 76.9 | 12 | 85.7 | |
| Female | 3 | 23.1 | 2 | 14.3 | |
| Smoking index | | | | | 0.085 |
| ≥ 400 | 5 | 38.5 | 10 | 71.4 | |
| < 400 | 8 | 61.5 | 4 | 28.6 | |
| Histopathology | | | | | 0.155 |
| Pure SCLC | 9 | 69.2 | 12 | 85.7 | |
| Mixed SCLC | 1 | 7.7 | 2 | 14.3 | |
| None | 3 | 23.1 | 0 | 0 | |
| cT-stage | | | | | 0.037 |
| T1 | 0 | 0 | 4 | 28.6 | |
| T2–T4 | 13 | 100 | 10 | 71.4 | |
| cTNM | | | | | 0.315 |
| I | 1 | 7.7 | 3 | 21.4 | |
| II–IIIa | 12 | 92.3 | 11 | 78.6 | |
| pT-stage | | | | | 0.010 |
| T0 | 3 | 23.1 | 0 | 0 | |
| T1 | 7 | 53.8 | 3 | 21.4 | |
| T2–T4 | 3 | 23.1 | 14 | 78.6 | |
| pN-stage | | | | | 0.148 |
| N0–1 | 10 | 76.9 | 7 | 50.0 | |
| N2 | 3 | 23.1 | 7 | 50.0 | |
| Surgery method | | | | | 0.557 |
| Segmentectomy | 0 | 0 | 1 | 7.1 | |
| Lobectomy | 8 | 61.5 | 8 | 57.1 | |
| Bilolobectomy | 0 | 0 | 1 | 7.1 | |
| Pneumonectomy | 5 | 38.5 | 4 | 28.6 | |
| Radiotherapy | | | | 7.1 | 0.050 |
| Yes | 5 | 38.5 | 1 | | |
| No | 8 | 61.5 | 13 | 92.9 | |
| PCI | | | | | 0.017 |
| Yes | 0 | 0 | 5 | 35.7 | |
| No | 13 | 100 | 9 | 64.3 | |

group A: neoadjuvant chemtherapy; group B: adjuvant chemotherapy; SCLC: small lung cell cancer; mixed SCLC: squamous cell carcinoma and small cell carcinoma

### Efficacy assessment

In our cohort, 13 patient received neoadjuvant chemotherapy. Pathological evaluation revealed nine cases of single SCLC and one case of mixed SCLC; in three cases, no cancerous cells were found. The pathological complete remission (PCR) rate reached 23.08%. In view of the small-scale nature of our study, TRG was categorized into three grades; three patients were confirmed as having G0 disease. Statistical analysis results showed that the DFS of G0 patients was similar to that of than G1-2 patients (median 16.267 versus 20.100 months, $P$ = 0.956).

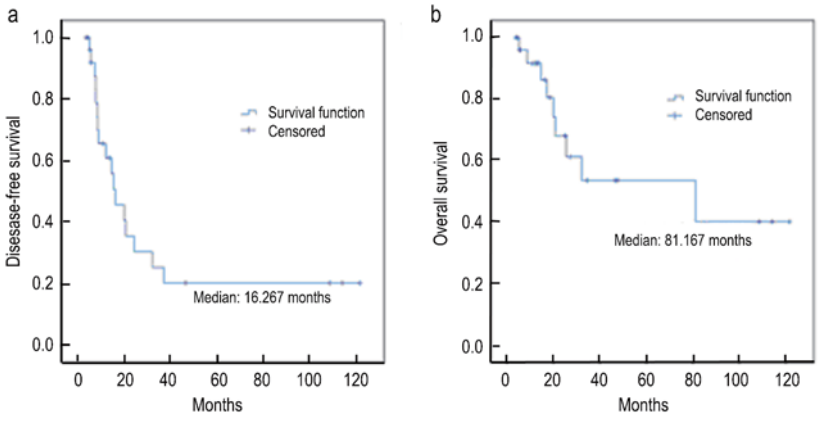


Fig. 1 Kaplan-Meier survival curves for 27 patients with limited-disease small cell lung cancer after surgical resection. (a) Disease-free survival; (b) Overall survival

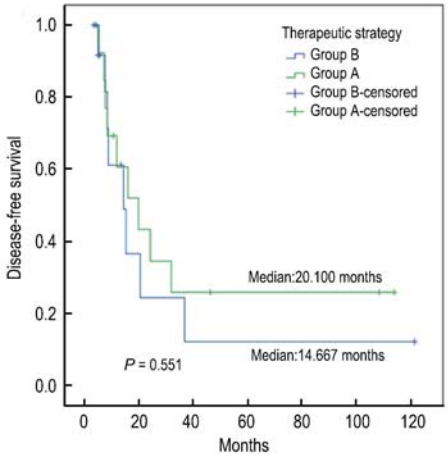


Fig. 2 Comparison of disease-free survival in patients with limited-disease small cell lung cancer between group A and group B

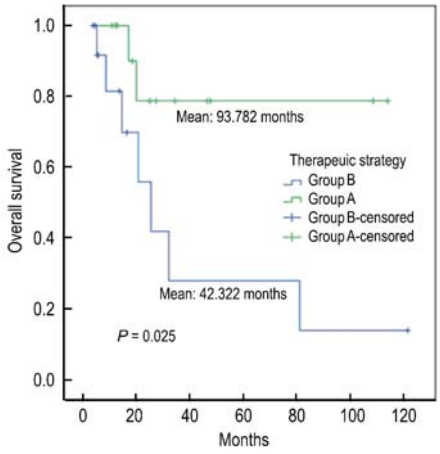


Fig. 3 Comparison of overall survival in patients with limited-disease small cell lung cancer between group A and group B

However, G0 patients were associated with better, albeit not statistically significant, OS than G1-2 patients (mean, 61.222 versus 31.213 months, $P = 0.311$).

## Discussion

Although chemotherapy represents the mainstay treatment option for LD-SCLC [14–15], surgical treatment still plays a crucial role. More attention is being paid to multimodal therapies for SCLC, and many studies have shown that resection therapy in the multimodal treatment setting is associated with less local relapse and increased survival benefits [16–18]. A meta-analysis of 13 randomized control trials of non-small cell lung cancer (NSCLC) patients, revealed than neoadjuvant chemotherapy combined with surgery could significantly prove the OS of patients with operable NSCLC [17]. However, surgical resection combined with neoadjuvant therapy is not feasible for all patients with LD-SCLC.

Hara *et al* [19] reported that, in patients with LD-SCLC, preoperative chemotherapy combined with subsequent surgery resulted in a better survival outcome than an initial surgery followed by adjuvant chemotherapy (5-year rate, 42% versus 33%). In addition, surgical resection after neoadjuvant chemotherapy may represent the optimal treatment choice for resectable stage III SCLC (particularly for patients with N2-positive disease). It is encouraging that neoadjuvant treatment extends the life of LD-SCLC patients undergoing surgical resection. Preoperative chemotherapy shrinks solid tumors, reduces the rate of recurrence, and prevents potential metastasis. As a result, the down-staging and subsequent tumor-removal rates are improved. We believe that pre- and post-operative chemotherapy in combination with surgery result in improved outcome due to the effects of the preoperative chemotherapy.

The TRG system is frequently used to evaluate the efficacy of neoadjuvant chemotherapy in esophageal carcinoma and gastroesophageal junction tumors [8–10, 20–21]; it is also a valuable survival prediction tool for patients with rectal cancer [22–23]. There is currently much debate regarding the standards in the TRG system. Some

Table 2 Univariate survival analyses on enrolled 27 patients

| Variate | *n* | DFS | | OS | |
|---|---|---|---|---|---|
| | | 95% CI (median) | *P* value | 95% CI (mean) | *P* value |
| Age (years) | | | 0.207 | | 0.002 |
| ≥ 65 | 5 | 8.351–9.782 (9.067) | | 8.310–25.103 (16.707) | |
| < 65 | 22 | 9.156–23.377 (16.267) | | 57.301–109.323 (83.312) | |
| Gender | | | 0.594 | | 0.970 |
| Male | 22 | 8.435–22.631 (15.533) | | 42.355–96.784 (69.570) | |
| Female | 5 | 7.631–33.969 (33.964) | | 20.395–35.191 (27.793) | |
| Smoking index | | | 0.670 | | 0.676 |
| ≥ 400 | 15 | 2.912–28.155 (15.533) | | 32.344–92.434 (62.389) | |
| < 400 | 12 | 8.701–23.833 (16.267) | | 46.138–111.163 (78.650) | |
| Histopathology | | | 0.923 | | 0.196 |
| Pure SCLC | 21 | 10.683–29.517 (20.100) | | None | |
| Mixed SCLC | 3 | 7.206–17.128 (12.167) | | None | |
| None | 3 | 0.000–33.124 (16.267) | | None | |
| cT-stage | | | 0.532 | | 0.506 |
| T1 | 4 | None | | 0.000–111.143 (50.983) | |
| T2–T4 | 23 | 5.931–23.402 (14.667) | | 47.976–101.240 (74.593) | |
| cTNM | | | 0.354 | | 0.875 |
| I | 4 | 0.000–84.787 (37.133) | | 31.795–117.255 (74.525) | |
| II–IIIa | 23 | 10.091–20.976 (15.533) | | 42.362–97.711 (70.037) | |
| pT-stage | | | 0.812 | | 0.288 |
| T0 | 3 | 0.000–33.124 (16.267) | | None | |
| T1 | 10 | 14.578–27.022 (20.800) | | None | |
| T2–T4 | 14 | 7.016–17.317 (12.167) | | None | |
| pN-stage | | | 0.036 | | 0.094 |
| N0–1 | 17 | 6.037–42.897 (24.467) | | 58.011–110.213 (84.112) | |
| N2 | 10 | 1.976–16.155 (9.067) | | 17.518–30.629 (23.876) | |
| PCI | | | 0.886 | | 0.189 |
| Yes | 5 | 0.000–27.621 (9.067) | | 0.000–84.525 (42.196) | |
| No | 22 | 9.009–23.525 (16.267) | | 51.140–105.358 (78.249) | |
| Therapeutic strategy | | | 0.551 | | 0.025 |
| Group A | 13 | 7.254–32.945 (20.100) | | 68.768–118.797 (93.782) | |
| Group B | 14 | 6.140–23.193 (14.667) | | 14.890–69.754 (42.322) | |
| TRG | | | 0.956 | | 0.311 |
| G0 | 3 | 0.000–33.124 (16.267) | | No CI (61.222) | |
| G1–2 | 10 | 2.972–37.228 (20.100) | | No CI (31.213) | |

CI: confidence interval; DFS: disease-free survival; OS: overall survival

experts recommend categorizing TRG into three grades [9], while others recommend four (G0, 0%; G1, 1%–10%; G2, 11%–50%; G3, > 50%) [10], or even five grades [24]. In this study, we prudently took the characteristics of our samples into consideration and chose to use three, rather than four or five, grades. Patients in the G0 group demonstrated a significantly greater survival benefit than patients in the other groups. While our survival evaluation did not show a significant difference in survival between patients in the G0 and G1-2 subgroups, there was a trend towards improved OS in the G0 subgroup. This may be explained by the high PCR rate in the patients who received preoperative chemotherapy. In studies of NSCLC, PCR has been shown to be a powerful prognostic factor for survival; it is also associated with better clinical outcome following neoadjuvant chemotherapy or chemoradiotherapy. Neoadjuvant therapy has been proven to prolong long-term local control rates and reduce progression in patients with locally advanced NSCLC (N2-positive) [25–26]. Considering that SCLC is generally sensitive to chemoradiotherapy, we believe that similar results may be achieved with neoadjuvant treatment of SCLC. Additionally, it has been shown that 60–90% of patients with LD-SCLC and 40-70% of patients with extensive disease respond to first-line chemotherapy [27]. All of the patients who achieved PCR received the etoposide and cisplatin (EP) regimen. Effective preoperative chemotherapy could diminish the pathological stage; an earlier stage is associated with a better prognosis. However, patients who received chemotherapy as a second-line treatment only and patients with mixed tumors did not achieve PCR.

In LD-SCLC, PCI has been proven improve survival

outcomes in patients who achieve complete response [28–29]. However in this study, there was no significant difference in DFS between patients who underwent PCI and those who did not ($P$ = 0.886). On the contrary, patients who did not undergo PCI appeared to have a slightly better OS than patients who underwent PCI ($P$ = 0.189). Some studies [28, 30] have reported that PCI resulted in long-lasting neurotoxicity and potentially deleterious effects that negatively affected survival. Lee *et al* [30] showed that in cases of severe neurotoxicity, no PCI was superior to PCI. In addition, in a recent meta-analysis, PCI had a detrimental effect on the OS of patients with extensive-disease SCLC [30], including NSCLC [31]. Therefore, PCI should be used with caution.

Our study has some clear limitations. The retrospective nature and the small cohort size reduced the statistical power, and may have introduced confounding factors and biases. In spite of these limitations, our evaluation is authentic. In an upcoming prospective controlled study, we will focus on more factors, including PCI and adjuvant thoracic radiation therapy.

### Conclusion

Neoadjuvant chemotherapy combined with surgical resection results in a significant survival benefit (OS) and is a feasible treatment for patients with LD-SCLC. Our results, based on the TRG system, indicate that patients who receive neoadjuvant chemotherapy and who have no residual cancer after surgery will attain the best survival outcome.

### Conflicts of interest

The authors indicated no potential conflicts of interest.

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