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Methods: Using the Surveillance, Epidemiology, and End Results registry, we identified 2,453 patients with early stage SCLC (1,295 women and 1,158 men) who had complete clinical information between 2004 and 2015. The Kaplan-Meier analysis was used to determine the propensity score based on the characteristics of patients with early stage SCLC. LCSS was compared between patients treated with surgery and non-surgery after adjusting, stratifying, or matching patients with early stage SCLC. In addition, we compared the effects of chemotherapy and radiotherapy on LCSS in patients with early stage SCLC.

Results: Overall, 687 (28.0%) and 1,766 (72.0%) patients with early stage SCLC did and did not undergo surgery, respectively. Kaplan-Meier analysis demonstrated a statistically significant difference in survival curves between the surgery and non-surgery groups (log-rank p<0.001). Compared with the non-surgery group, the LCSS of the surgery group was better (hazard ratio [HR]:0.494, 95% confidence interval [CI]:0.415–0.587, p<0.001) in patients with early stage SCLC when using a Cox model for multivariate analysis. There was no statistically significant difference (p=0.847) in LCSS between patients with early stage SCLC with and without chemotherapy in the multivariate analysis. Radiotherapy had favorable effects on LCSS (HR: 0.579, 95% CI: 0.500–0.671, p<0.001) in patients with early stage SCLC using multivariate analysis.

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patients are diagnosed at a stage in which their disease may be curable. \(^4\) Patients with early stage SCLC who underwent surgery had a reported five-year survival rate of 40% to 60%. \(^5\)–\(^9\)

Historically, SCLC was treated by surgery. However, the Medical Research Council performed a trial\(^10\) in the 1960s that demonstrated the poor survival of patients who underwent surgery. This outcome resulted in the abandonment of surgery and the use of chemotherapy as a standard method for SCLC treatment. Subsequently, two meta-analyses\(^11\),\(^12\) reported that systemic chemotherapy in combination with thoracic radiation improved survival, a treatment that has become the standard for patients with SCLC.

However, the treatment of SCLC remains controversial. Some institutions have reported good results in patients with early stage SCLC who received surgery.\(^5\),\(^13\) Other studies have reported favorable results in patients with stage III SCLC who be interfered with surgery.\(^7\),\(^14\) Therefore, this study aimed to investigate the effects of surgical resection on lung cancer-specific survival (LCSS) in patients with early stage SCLC. We also analyzed the effect of adjuvant chemotherapy and radiotherapy on the LCSS in these patients.

**Methods**

**Data source**

The data used in this study were from the Surveillance, Epidemiology, and End Results (SEER) database. The SEER database is sponsored by the National Cancer Institute of the US and provides registry information on cancer including pathological type, patient survival, surgery, and adjuvant therapy since 1973.

**Study population**

We limited the cohort to patients with early stage SCLC diagnosed from 2004 to 2015. All early stage SCLC patients were staged using American Joint Committee on Cancer with stage I or IIa (stage T1-2N0M0) disease. Patients who underwent surgery were staged pathologically and those without surgery had clinic staging. Complete patient information was available in the SEER database.

**Covariates**

The baseline characteristics based on 17 covariates included age, sex, race, tumor size, TNM stage, tumor location, differentiated grade, laterality, surgery, radiotherapy, chemotherapy, insurance status, year of diagnosis, marital status, geographic region, high school education, and median household income.

To better analyze the effects of adjuvant therapy on LCSS, we created a new covariate called adjuvant therapy, defined as patients who received one or both treatments (chemotherapy, radiotherapy or chemoradiotherapy).

**Statistical analyses**

All data were analyzed using IBM SPSS, version 20.0 (IBM Corp, Armonk, NY, USA). Kaplan-Meier analysis was used to compare survival between the surgery and non-surgery groups. Propensity score methods were used to control for potential differences in baseline characteristics of the included patients. Cox regression was performed to assess the balance of the baseline covariates of the two groups after adjusting for the estimated propensity scores.

**Results**

**Study cohort characteristics**

We identified 2,453 patients with early stage SCLC, of whom 687 (28.0%) underwent surgery as a primary treatment and 1,766 (72.0%) did not between 2004 and 2015. Table 1 shows the baseline characteristics of all patients identified through the SEER database. The results of Kaplan-Meier analyses demonstrated statistically significant differences in LCSS between the two groups with regard to age \((p<0.001)\), sex \((p=0.007)\), tumor size \((p<0.001)\), TNM stage \((p<0.001)\), radiotherapy \((p=0.001)\), chemotherapy \((p=0.026)\), insurance status \((p<0.001)\), adjuvant therapy \((p=0.007)\), and year of diagnosis \((p<0.001)\). However, no significant differences in LCSS were observed with respect to race \((p=0.396)\), tumor location \((p=0.698)\), differentiated grade \((p=0.063)\), laterality \((p=0.611)\), marital status \((p=0.426)\), geographic region \((p=0.069)\), high school education \((p=0.138)\), and median household income \((p=0.470)\) (Table 1).

A Cox model for multivariate analysis including the above significant covariates (TNM stage was excluded due to covariates tumor size and TNM stage linearly related) showed statistically significant differences for age \((p<0.001)\), sex \((p=0.008)\), tumor size \((p=0.002)\), surgery \((p=0.001)\), radiotherapy \((p=0.001)\), and year of diagnosis \((p=0.001)\). Covariates such as chemotherapy \((p=0.942)\), insurance status \((p=0.495)\), and adjuvant therapy \((p=0.839)\) did not differ significantly (Table 2). Subsequent analysis using a new Cox model including five covariates (age, sex, tumor size, surgery, and radiotherapy) revealed statistically
Table 1  Baseline characteristics of patients treated with surgery or non-surgery in the Surveillance, Epidemiology and End Results (SEER) Program, 2004–2015

| Characteristics | Early stage SCLC | Surgery | Non-surgery | ρ |
|-----------------|------------------|---------|-------------|---|
|                 | Number %         | Number %| Number %    |   |
| Age, year       |                  |         |             | <0.001 |
| <45             | 14               | 0.6     | 4           | 0.6 |
| ≥45, <55        | 150              | 6.1     | 35          | 5.1 |
| ≥55, <65        | 490              | 20      | 177         | 25.8 |
| ≥65, <75        | 940              | 38.3    | 300         | 43.6 |
| ≥75             | 859              | 35      | 171         | 24.9 |
| Sex             |                  |         |             | 0.007 |
| Female          | 1295             | 52.8    | 375         | 54.6 |
| Male            | 1158             | 47.2    | 312         | 45.4 |
| Race            |                  |         |             | 0.396 |
| White           | 2172             | 88.5    | 627         | 91.3 |
| Black           | 203              | 8.3     | 39          | 5.7 |
| Others          | 75               | 3.1     | 20          | 2.9 |
| Unknown         | 3                | 0.1     | 1           | 0.1 |
| Tumor size, cm  |                  |         |             | <0.001 |
| ≤1              | 162              | 6.6     | 97          | 14.1 |
| >1, ≤2          | 759              | 30.9    | 302         | 44  |
| >2, ≤3          | 739              | 30.2    | 176         | 25.6 |
| >3, ≤4          | 473              | 19.3    | 75          | 10.9 |
| >4, ≤5          | 317              | 12.9    | 36          | 5.3 |
| Unknown         | 3                | 0.1     | 1           | 0.1 |
| TNM stage       |                  |         |             | <0.001 |
| Stage Ia1       | 162              | 6.6     | 97          | 14.1 |
| Stage Ia2       | 759              | 30.9    | 302         | 44  |
| Stage Ia3       | 739              | 30.2    | 176         | 25.6 |
| Stage Ib        | 473              | 19.3    | 75          | 10.9 |
| Stage IIa       | 317              | 12.9    | 36          | 5.3 |
| Unknown         | 3                | 0.1     | 1           | 0.1 |
| Tumor location  |                  |         |             | 0.698 |
| Upper lobe      | 1377             | 56.2    | 421         | 61.3 |
| Middle lobe     | 177              | 7.2     | 57          | 8.3 |
| Lower lobe      | 719              | 29.3    | 192         | 27.9 |
| NOS             | 64               | 2.6     | 7           | 1  |
| Overlapping lesion | 8              | 0.3     | 2           | 0.3 |
| Main bronchus   | 108              | 4.4     | 8           | 1.2 |
| Differentiated grade |            |         |             | 0.063 |
| Grade I         | 12               | 0.5     | 7           | 1  |
| Grade II        | 27               | 1.1     | 16          | 2.3 |
| Grade III       | 413              | 16.8    | 206         | 30  |
| Grade IV        | 604              | 24.6    | 222         | 32.3 |
| Unknown         | 1397             | 57      | 236         | 34.4 |

(Continued)
| Characteristics                        | Early stage SCLC | Surgery | Non-surgery | p     |
|---------------------------------------|------------------|---------|-------------|-------|
|                                       | Number %         | Number %| Number %    |       |
| Laterality                            |                  |         |             |       |
| Right-origin of primary               | 1389             | 56.6    | 406         | 59.1  |
|                                       | 1059             | 43.2    | 280         | 40.8  |
| Left-origin of primary                |                  |         |             |       |
| Paired site, but no information       | 2                | 0.1     | 1           | 0.1   |
| concerning laterality                 |                  |         |             |       |
| Not a paired site                     | 3                | 0.1     | 0           | 0.1   |
| Radiotherapy                          |                  |         |             |       |
| No                                    | 1207             | 49.2    | 535         | 77.9  |
|                                       | 1246             | 50.8    | 152         | 22.1  |
| Yes                                   |                  |         |             |       |
| Chemotherapy                          |                  |         |             |       |
| No                                    | 826              | 33.7    | 284         | 41.3  |
|                                       | 1627             | 66.3    | 403         | 58.7  |
| Yes                                   |                  |         |             |       |
| Adjuvant therapy                      |                  |         |             |       |
| None                                  | 629              | 25.6    | 273         | 39.7  |
|                                       | 1049             | 42.8    | 141         | 13.4  |
| Chemoradiotherapy                     |                  |         |             |       |
| Chemotherapy only                     | 578              | 23.6    | 262         | 45.3  |
| Radiotherapy only                     | 197              | 8       | 11          | 5.6   |
| Insurance status                      |                  |         |             |       |
| Medicaid                              | 242              | 9.9     | 56          | 8.2   |
|                                       | 627              | 25.5    | 176         | 25.6  |
| uninsured                             | 31               | 1.3     | 9           | 1.3   |
| Unknown                               | 1553             | 63.3    | 446         | 64.9  |
| Insured                               |                  |         |             |       |
| Marital status                        |                  |         |             |       |
| Married                               | 1195             | 48.7    | 364         | 53    |
|                                       | 272              | 11.1    | 72          | 10.5  |
| Single                                | 272              | 11.1    | 72          | 10.5  |
| Divorced                              | 354              | 14.4    | 98          | 14.3  |
| Widowed                               | 541              | 22.1    | 127         | 18.5  |
| Unknown                               | 90               | 3.7     | 25          | 3.6   |
| Unmarried or Domestic Partner         | 1                | 0       | 1           | 0.1   |
| Year of diagnosis                     |                  |         |             |       |
| 2004–2007                             | 807              | 32.9    | 230         | 33.5  |
|                                       | 787              | 32.1    | 226         | 32.9  |
| 2008–2011                             | 859              | 35      | 231         | 33.6  |
| 2012–2015                             |                  |         |             |       |
| Geographic region                     |                  |         |             |       |
| East                                  | 1284             | 52.3    | 395         | 57.5  |
|                                       | 777              | 31.7    | 197         | 28.7  |
| Northwest                             | 321              | 13.1    | 77          | 11.2  |
| North                                 | 71               | 2.9     | 18          | 2.6   |
| Southwest                             |                  |         |             |       |
| High school education                 |                  |         |             |       |
| ≥21                                   | 449              | 18.3    | 129         | 18.8  |
|                                       | 739              | 30.1    | 186         | 27.1  |

(Continued)
significant differences for age (p<0.001), sex (p=0.014), tumor size (p=0.006), surgery (p<0.001), and radiotherapy (p<0.001) (Table 3).

**Comparison of disease-specific mortality and median survival time between the surgery and non-surgery groups**

The overall lung cancer-specific mortality rate in patients with early stage SCLC was 35.8% (879/2453). The mortality rates were 35.2% (242/687) and 36.1% (637/1766) for the surgery and non-surgery groups, respectively. The overall median survival time for patients with early stage SCLC was 17 months. The median survival times in the surgery and non-surgery groups were 26 and 15 months, respectively. The survival between the surgery and non-surgery groups were 26 and 15 months, respectively. The survival advantage (log-rank p<0.001) in the surgery group persisted in patients aged <75 years (Figure 1B). The survival advantage (log-rank p<0.001) in the surgery group persisted in patients aged ≥75 years (Figure 1C). In addition, the survival (log-rank p<0.001) of the surgery group was better than that of the non-surgery group for patients with tumor size T1 (≤3 cm) (Figure 1D). The survival advantage (log-rank p=0.002) in the surgery group persisted in patients with tumor size T2 (3 cm< and ≤5 cm) (Figure 1E). Our data demonstrated the significant effect of surgery on disease-specific survival in patients with early stage SCLC.

**Comparison of the effects of adjuvant therapy in patients with early stage SCLC**

Kaplan–Meier analysis showed a statistically significant difference (p=0.026) in the LCSS in patients with early stage SCLC who received chemotherapy (Table 1). However, this difference disappeared in the Cox model (p=0.847) (Table 2). Similarly, there was a significant difference (p=0.031) in LCSS in patients with early stage SCLC who received adjuvant therapy (Table 1), which also disappeared in the Cox model (p=0.839) (Table 2).

Kaplan-Meier analysis also revealed a statistically significant difference (p=0.001) in LCSS in patients with early stage SCLC who received radiotherapy by (Table 1). In a Cox model including nine covariates, the HR (95% CI) was 0.572 (0.479–0.682, p<0.001) for patients who received radiotherapy compared to those without (Table 2). After adjusting for age, sex, tumor size, surgery, and radiotherapy, the HR (95% CI) was 0.579 (0.500–0.671, p<0.001) in patients who received radiotherapy (Table 3).

The effects of radiotherapy on LCSS are also shown in Table 6. The HR (95% CI) of patients with radiotherapy was 0.804 (0.704–0.918, p=0.001) compared to patients without radiotherapy. Similarly, compared to patients

| Characteristics | Early stage SCLC | Surgery | Non-surgery | p |
|-----------------|-----------------|---------|-------------|---|
| Number %        | Number %        | Number %|             |   |
| 7–12            | 1083            | 319     | 764         |   |
| <7              | 182             | 53      | 129         |   |
| Median household income (dollar, in tens) | | | | |
| <38000          | 221             | 69      | 152         |   |
| 38000–47999     | 488             | 119     | 369         |   |
| 48000–62999     | 942             | 250     | 692         |   |
| >63000          | 802             | 249     | 553         |   |

**Table 1 (Continued).**

**Abbreviations:** SCLC, small-cell lung cancer; NOS, not otherwise specified.
Table 2 Multivariate analysis using a cox proportional hazards model in patients with early stage SCLC

| Variable              | Multivariable analysis* |
|-----------------------|--------------------------|
|                       | HR  | 95% CI          | p    |
| Age, year             |     |                 |      |
| <45                   | Reference            |     | <0.001 |
| ≥45, <55              | 4.961 | 1.208–20.374 | 0.026 |
| ≥55, <65              | 5.008 | 1.238–20.257 | 0.024 |
| ≥65, <75              | 5.618 | 1.391–22.681 | 0.015 |
| ≥75                   | 7.381 | 1.824–29.870 | 0.005 |
| Sex                   |     |                 |      |
| Female                | Reference           |     | 0.008  |
| Male                  | 1.201  | 1.050–1.374 |      |
| Tumor size, cm        |     |                 |      |
| ≤1                    | Reference           |     | 0.002  |
| >1, ≤2                | 1.18   | 0.868–1.604  |      |
| >2, ≤3                | 1.217  | 0.893–1.658  | 0.292 |
| >3, ≤4                | 1.346  | 0.975–1.858  | 0.213 |
| >4, ≤5                | 1.77   | 1.268–2.471  | 0.071 |
| Unknown               | 1.192  | 1.063–8.735  | 0.001 |
| Surgery               |     |                 |      |
| No                    | Reference           |     | <0.001 |
| Yes                   | 0.499  | 0.420–0.594  |      |
| Radiotherapy          |     |                 |      |
| No                    | Reference           |     | <0.001 |
| Yes                   | 0.552  | 0.411–0.742  |      |
| Chemotherapy          |     |                 |      |
| No                    | Reference           |     | 0.942  |
| Yes                   | 0.993  | 0.822–1.200  |      |
| Adjuvant therapy      |     |                 |      |
| None                  | Reference           |     | 0.839  |
| Chemoradiotherapy     | 1.035  | 0.742–1.445  |      |
| Insurance status      |     |                 |      |
| Medicaid              | 1.288  | 0.724–2.290  | 0.495 |
| uninsured             | 0.869  | 0.621–1.215  | 0.639 |
| Unknown               | 0.9    | 0.709–1.142  | 0.39  |
| Insured               | 0.975  | 0.957–1.417  | 0.411 |
|                      | Reference           |     | 0.386  |
| Year of diagnosis     |     |                 |      |
| 2004–2007             | 1.255  | 1.828–3.075  | <0.001|
| 2008–2011             | 2.371  | 0.078        | <0.001|
| 2012–2015             | 1.858  | 2.139–26.761 |      |

Notes: *Multivariate analysis for age, sex, tumor size, surgery, radiotherapy, chemotherapy, insurance status, adjuvant therapy and year of diagnosis.

Abbreviations: SCLC, small-cell lung cancer; HR, hazard ratio; CI, confidence interval.

Without radiotherapy, the HR (95% CI) was 0.804 (0.683–0.947, p=0.009) among patients aged <75 years. However, compared to patients without radiotherapy aged ≥75 years, there was no significant difference (p=0.102) in LCSS. Among patients with T1 (tumor size ≤3 cm), the HR (95% CI) of patients who received radiotherapy was 0.830 (0.703–0.980, p=0.028) compared to those without radiotherapy. Compared to patients without radiotherapy, the HR (95% CI) of patients with radiotherapy was 0.705 (0.565–0.880, p=0.002) in patients with T2 (3 cm< and ≤5 cm). In addition, the HR (95% CI) of patients with radiotherapy was 0.544 (0.463–0.639, p<0.001) compared to those without radiotherapy or surgery. However, there was no statistically significant difference (p=0.079) in LCSS regardless of radiotherapy among patients who underwent surgery (Table 5).

The effects of radiotherapy on the survival curves are shown in Figure 2. In patients with early stage SCLC, the survival curve (log-rank p<0.001) of patients with radiotherapy was better than that in those without radiotherapy (Figure 2A). However, there was no statistically significant difference in survival curve (log-rank p>0.05) between patients with and without radiotherapy among those aged ≥75 years (Figure 2B). However, the survival curve (log-rank p<0.05) of patients with radiotherapy was better than that of those without radiotherapy among those aged <75 years (Figure 2C). Among patients with T1 (tumor sizes ≤3 cm) (log-rank p<0.05) and T2 (3 cm< and ≤5 cm), the survival curves of patients with radiotherapy were better than those of patients without radiotherapy (log-rank p<0.05) (Figure 2D and E). In patients with surgery, there was no significant difference in survival curves (log-rank p>0.05) between patients with and without radiotherapy (Figure 2F). However, among those without surgery, the survival curve (log-rank p<0.001) of patients with radiotherapy was better than that of those without radiotherapy (Figure 2G).

Comparison of the effects of treatment combinations in patients with early stage SCLC

According to the patient’s adjuvant therapy plans, we divided the patients with early stage SCLC into four cohorts: patients with chemoradiotherapy (cohort 1), patients without any adjuvant therapy (cohort 2), patients with chemotherapy only (cohort 3) and patients with chemoradiotherapy plus without any adjuvant therapy (cohort 4). Subsequently, we set up treatment combinations: non-surgery plus chemoradiotherapy group and surgery plus chemoradiotherapy group in cohort 1, non-surgery plus no adjuvant therapy group and surgery plus no adjuvant therapy group in cohort 2, non-
surgery plus chemotherapy only group and surgery plus chemotherapy only group in cohort 3 as well as non-surgery plus chemoradiotherapy group and surgery plus no adjuvant therapy group in cohort 4. In all cohorts, there were significant differences in survival curves and log-rank tests between the two groups in the same cohort (Figure 3). The survival curve (log-rank \(p<0.001\)) of the surgery plus chemoradiotherapy group was better than that of the non-surgery plus no adjuvant therapy group in cohort 2 (Figure 3B), and the survival curve (log-rank \(p<0.001\)) of the surgery plus chemotherapy only group was better than that of the non-surgery plus chemotherapy only group in cohort 3 (Figure 3C). In addition, the survival curve (log-rank \(p=0.005\)) of the surgery plus no adjuvant therapy group was also better than that of the non-surgery plus chemoradiotherapy group in cohort 4 (Figure 3D).

Analogous results were showed in Table 7 by univariate analysis. Compared to the non-surgery plus chemoradiotherapy group, the HR (95% CI) of the surgery plus chemoradiotherapy group was 0.581 (0.429–0.787, \(p<0.001\)) in cohort 1. The HR (95% CI) of the surgery plus no adjuvant therapy group was 0.401 (0.300–0.536, \(p<0.001\)) compared to the non-surgery plus chemotherapy only group in cohort 2. The HR (95% CI) of the surgery plus chemotherapy only group was 0.462 (0.353–0.665, \(p=0.001\)) compared to the non-surgery plus chemotherapy only group in cohort 3. The HR (95% CI) of the surgery plus no adjuvant therapy group was 0.709 (0.557–0.903, \(p=0.004\)).

Table 3 Unvariable and multivariable analyses on LCSS in patients with early stage SCLC

| Variable   | Univariable analysis | Multivariable analysis* |     |     |
|------------|----------------------|-------------------------|-----|-----|
|            | HR                   | 95% CI                  | \(p\) | HR  | 95% CI                  | \(p\) |
| Age, year  |                      |                         |     |     |
| <45        | Reference            |                         |     |     |
| ≥45, <55   | 4.346                | 1.061–17.796            | 0.041 | 4.477 | 1.092–18.351            | 0.037 |
| ≥55, <65   | 4.158                | 1.031–16.771            | 0.045 | 4.615 | 1.143–18.638            | 0.032 |
| ≥65, <75   | 4.695                | 1.168–18.878            | 0.029 | 5.418 | 1.345–21.820            | 0.017 |
| ≥75        | 6.492                | 1.613–26.131            | 0.008 | 6.9  | 1.711–27.826            | 0.007 |
| Sex        |                      |                         |     |     |
| Female     | Reference            |                         | 0.007 | Reference | 1.184 | 1.035–1.354 |
| Male       | 1.199                | 1.050–1.370             |     |     |
| Tumor size, cm |                |                         |     |     |
| ≤1        | Reference            |                         |     |     |
| >1, ≤2    | 1.299                | 0.959–1.759             | 0.091 | 1.183 | 0.870–1.607             | 0.284 |
| >2, ≤3    | 1.363                | 1.006–1.847             | 0.045 | 1.175 | 0.863–1.600             | 0.307 |
| >3, ≤4    | 1.597                | 1.167–2.187             | 0.003 | 1.319 | 0.956–1.820             | 0.092 |
| >4, ≤5    | 1.963                | 1.422–2.710             | 0    | 1.685 | 1.208–2.349             | 0.002 |
| Unknown   | 1.129                | 0.156–8.178             | 0.904 | 1.14  | 0.156–8.315             | 0.897 |
| Surgery   |                      |                         |     |     |
| No        | Reference            |                         |     |     |
| Yes       | 0.59                 | 0.508–0.686             | <0.001 | Reference | 0.494 | 0.415–0.587 |
| Radiotherapy |                |                         |     |     |
| No        | Reference            |                         |     |     |
| Yes       | 0.804                | 0.704–0.918             | 0.001 | Reference | 0.579 | 0.500–0.671 |
| Notes:     | *Multivariate analysis for age, sex, tumor size, radiotherapy, surgery and chemotherapy.  
Abbreviations: LCSS, lung cancer-specific survival; SCLC, small-cell lung cancer; HR, hazard ratio; CI, confidence interval.

Table 4 Association with cancer-specific mortality and median survival time among patient groups (SEER database, 2004–2015)

| Group        | Mortality, % (n/N) | Median survival time (months) |
|--------------|-------------------|------------------------------|
| Overall      | 35.8% (879/2453)  | 17                           |
| Non-surgery  | 35.2% (242/687)   | 15                           |
| Surgery      | 36.1% (637/1766)  | 26                           |
| Notes:       | SEER, Surveillance, Epidemiology and End Results.  
Abbreviations: SEER, Surveillance, Epidemiology and End Results.
compared to the non-surgery plus chemoradiotherapy group in cohort 4.

**Discussion**

Currently, chemoradiotherapy is the standard treatment for early stage SCLC, providing a median overall survival of 16–20 months. However, the optimal treatment of early stage SCLC remains controversial. An increasing number of studies suggest that surgical treatment can improve survival outcomes in patients with SCLC, especially in early stage disease. Retrospective studies have reported favorable outcomes for surgery in
A growing number of patients with stage I SCLC receive surgical treatment, resulting in a favorable overall median survival of 29–91 months. The present study evaluated the survival outcomes of surgery versus non-surgery in patients with early stage SCLC, finding that surgery resulted in a better LCSS than that of non-surgery. To further analyze the effect of surgery on LCSS in elderly patients with early stage SCLC, we divided the age covariates into groups according to age (<75 years), tumor size (T1 or T2), and surgery (yes or no) to analyze the effects of surgery on LCSS in patient groups by univariate analysis. Compared to that in non-radiotherapy patients, the LCSS of patients with radiotherapy was significantly better among those aged ≥75 years. Similarly, the LCSS of patients with radiotherapy was significantly better than that in those without radiotherapy and without surgery. However, among patients aged ≥75 years or with surgery, there was no advantage for radiotherapy compared to non-radiotherapy. In addition, radiotherapy can provide a benefit in LCSS for radiotherapy patients, whether T1 or T2.

Patients with early stage SCLC might receive multiple treatments including surgery, radiotherapy and chemotherapy. This result is consistent with those of the above studies.

At present, chemotherapy is the main treatment for early stage SCLC. We analyzed the effect of chemotherapy on LCSS in patients with early stage SCLC. Univariate analysis revealed statistically significant differences in LCSS between chemotherapy and non-chemotherapy patients with early stage SCLC. However, a Cox model for multivariate analysis indicated no statistically significant difference in LCSS between these groups. In addition, we defined one or two rounds of chemotherapy and radiotherapy as adjuvant therapy. We found a significant difference in univariate analysis, which disappeared in multivariate analysis. According to these outcomes, chemotherapy did not provide significant survival benefits for patients with early stage SCLC. This result may provide a reference for clinicians to select appropriate treatment methods for these patients.

Because SCLC is radiosensitive, radiotherapy can provide local control for patients with SCLC. We analyzed the effect of radiotherapy on LCSS in patients with early stage SCLC. In univariate analysis, the LCSS of patients with radiotherapy was better than that in non-radiotherapy patients. A Cox model for multivariate analysis (included covariates: age, sex, tumor size, surgery, and radiotherapy) also revealed a better LCSS in patients with radiotherapy than that in non-radiotherapy patients. These results suggest that radiotherapy has a significant effect on LCSS in patients with early stage SCLC. The patients were further divided into groups according to age (≥75 or <75 years), tumor size (T1 or T2), and surgery (yes or no) to analyze the effects of radiotherapy on LCSS in univariate analysis. Compared to that in non-radiotherapy patients, the LCSS of patients with radiotherapy was significantly better among those aged <75 years. Similarly, the LCSS of patients with radiotherapy was significantly better than that in those without radiotherapy and without surgery. However, among patients aged ≥75 years or with surgery, there was no advantage for radiotherapy compared to non-radiotherapy. In addition, radiotherapy can provide a benefit in LCSS for radiotherapy patients, whether T1 or T2.

Patients with early stage SCLC might receive multiple treatments including surgery, radiotherapy and chemotherapy.
Figure 2 Comparison of the effects of radiotherapy on LCSS based on Kaplan–Meier analysis. (A) LCSS ($p=0.001$) in patients with early stage SCLC; (B) LCSS ($p>0.05$) in patients with age $\geq$ 75 years; (C) LCSS ($p<0.05$) in patients with age $<75$ years; (D) LCSS ($p<0.05$) in patients with T1 (tumor sizes $\leq 3$ cm); (E) LCSS ($p<0.05$) in patients with T2 (3 cm< sizes $\leq 5$ cm); (F) LCSS ($p>0.05$) in patients with surgery; (G) cancer-specific survival ($p<0.001$) in patients with non-surgery.

Abbreviations: LCSS, lung cancer-specific survival; SCLC, small-cell lung cancer.
Therefore, it was necessary to further discuss the significance of surgery in different treatment combinations. Due to the small number of patients undergoing surgery plus radiotherapy, we did not discuss it further. Our results showed that the combination comprising surgery was superior to the combination without surgery on LCSS in the same cohort. Moreover, surgical treatment was superior to chemoradiotherapy in patients with early stage SCLC (Figure 3D, Table 7). This study further indicates that surgical treatment is a better option for patients with early stage SCLC.

Due to its retrospective design, our study has some limitations. One is the lack of information showing the status of performance or other indicators of the patient’s physical condition. Another limitation is the lack of specific treatment information for the patient, such as chemotherapy regimen, radiation dose and method, and the surgical procedure. However, with the inclusion of 18 covariates and nearly 2,500 patients in our cohort, the present study represents a well-balanced analysis between surgery and non-surgical methods. Thus, in the absence of data from prospective trials, our findings provide useful information for the management of patients with early stage SCLC.

In summary, the prognosis of patients with early stage SCLC was related to a variety of factors. According to the results of our study, surgery was superior to non-surgery in patients with early stage SCLC; therefore, we recommend surgical resection as the more favorable choice. In addition, because radiotherapy may be beneficial for patients with early stage SCLC, it should be recommended, especially in patients not undergoing surgery and aged <75 years. Understanding this information is critical to the prognosis of patients with early stage SCLC and our findings help in determining the best treatment strategies for these patients.
Table 7 Comparison of the effects of treatment combinations on LCSS in patients with early stage SCLC by univariate analysis

| Treatment Combination       | Number | Univariable Analysis | HR   | 95%CI          | p     |
|-----------------------------|--------|----------------------|------|---------------|-------|
| Cohort 1                    |        |                      |      |               |       |
| Non-surgery plus Chemoradiotherapy | 908    | Reference            | 0.581| 0.429–0.787   | <0.001|
| Surgery plus Chemoradiotherapy | 141    |                      |      |               |       |
| Cohort 2                    |        |                      |      |               |       |
| Non-surgery plus No adjuvant therapy | 356  | Reference            | 0.401| 0.300–0.536   | <0.001|
| Surgery plus                |        |                      |      |               |       |
| No adjuvant therapy         | 273    |                      |      |               |       |
| Cohort 3                    |        |                      |      |               |       |
| Non-surgery plus Chemotherapy only | 316 | Reference           | 0.462| 0.353–0.605   | <0.001|
| Surgery plus Chemotherapy only | 262  |                      |      |               |       |
| Cohort 4                    |        |                      |      |               |       |
| Non-surgery plus Chemoradiotherapy | 908    | Reference            | 0.709| 0.557–0.903   | 0.005 |
| Surgery plus No adjuvant therapy | 273 |                      |      |               |       |

Abbreviations: LCSS, lung cancer-specific survival; SCLC, small-cell lung cancer; HR, hazard ratio; CI, confidence interval.

Abbreviation list
SCLC, small-cell lung cancer; SEER, Surveillance, Epidemiology and End Results; LCSS, lung cancer-specific survival; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent is waived.

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Disclosure
The authors declare there are no potential conflicts of interest related to this study.

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