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Surveillance Epidemiology and End Results Evaluation of the Role of Surgery for Stage I Small Cell Lung Cancer

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Introduction: This study was performed to evaluate the clinical outcomes of surgery for stage I small cell lung cancer (SCLC).

Methods: The National Cancer Institute Surveillance Epidemiology and End Results (SEER) database was analyzed to evaluate outcomes for patients with SCLC treated from 1988 to 2004. Patients with stage I disease were selected. Kaplan-Meier survival curves were constructed for overall survival (OS) and cause-specific survival for patient strata based on type of surgery and radiation use or nonuse. Although SEER does not provide chemotherapy details, it is assumed that most, if not all, of these patients received systemic therapy.

Results: A total of 1560 patients were identified as having stage I SCLC. Median age was 70 years (range 27–94 years). Two hundred forty-seven patients underwent lobectomy, 121 had local tumor excision/ablation, 10 had a pneumonectomy, and surgery was unknown in 21. One thousand one hundred sixty-one did not have any cancer-directed surgery. Of those who had lobectomy, 205 (83%) did not receive radiation therapy (RT), 38 (15%) did receive RT, and use of RT was unknown in 4 (2%).

For those who had lobectomy without RT ($n = 205$), 3- and 5-year OS was 58.1% (95% confidence interval [CI] 51.1–64.5%) and 50.3% (95% CI 43.1–57.1%), respectively. For those patients who had a lobectomy with RT ($n = 38$), 3- and 5-year OS was 64.9% (95% CI 45.5–78.9%) and 57.1% (95% CI 37.4–72.7%), respectively.

Conclusions: Surgery without RT seems to offer reasonable OS outcomes in a cohort of stage I patients who undergo lobectomy. These results should be considered with the understanding that systemic therapy information and margin status are not available from the SEER database.

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Small cell lung cancer (SCLC) accounts for 13 to 20% of all lung cancers,[1] with an estimated annual incidence of 22,000 to 34,000 cases per year.[2] Staging is typically dichotomized to "limited" or "extensive" stage disease, with limited stage disease typically defined as confined to the hemithorax of origin, mediastinum, and supraclavicular lymph nodes and able to be treated with a single radiotherapy port.[3,4] More recent studies and the National Comprehensive Cancer Network guidelines[5] use the American Joint Committee on Cancer tumor, node, metastasis staging for more precise stratification of disease extent. The International Association for the Study of Lung Cancer recommendations for staging of SCLC also note the significance of T and N stage on survival.[6]

For very early stage disease, initial randomized data favored the use of radiation versus surgery[7]; however, more modern studies have noted reasonable survival in node-negative patients who undergo resection and chemotherapy.[8–14] The Lung Cancer Study Group randomized trial failed to show improved survival for surgery compared with radiation after neoadjuvant therapy,[15] but this study has been criticized for using suboptimal chemotherapy, for excluding peripheral nodules (which are assumed to be T1N0 disease), and for allowance of subtotal resection in the surgical arm.[16]

In light of the above conflicting randomized and retrospective analyses, treatment for locally confined SCLC is the subject of ongoing randomized trials.[16] Currently, treatment for limited stage SCLC typically involves a combination of radiation and chemotherapy. However, for small lesions without lymph node involvement, expert consensus has recommended the consideration of curative-intent surgery.[2] National Comprehensive Cancer Network guidelines have also recommended lobectomy and mediastinal lymph node dissection followed by chemotherapy as the preferred treatment in patients who are clinically stage T1-2N0.[5] The American College of Chest Physicians guidelines noted that though there was inadequate evidence to support any categorical recommendation regarding surgery in early-stage patients, the authors "favor surgery in patients with node-negative disease with small tumor size (<3 cm)."[2] Mediastinoscopy, head computed tomography or magnetic resonance imaging, abdominal computed tomography, and bone scan should be performed (level 1A recommendation), and platinum based adjuvant chemotherapy was recommended (level 2C recommendation).[2]

To assist in characterizing outcomes for patients with stage I SCLC treated with surgical resection without radiotherapy in the community, the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database was investigated.[17] The SEER database is a large na-

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tional cancer database that combines state and city cancer registries that most recently involves >25% of the US cancer population.

PATIENTS AND METHODS

Patient Selection

After waiver from the Yale University School of Medicine Human Investigation Committee, the National Cancer Institute 1973–2004 SEER database was examined. Patients from 1973 to 1987 were not included in this analysis because they did not have adequate information regarding pathologic staging and lymph node dissection. Histology and site of disease are coded in SEER according to the International Classification of Diseases (ICD) for Oncology, Edition 3 (ICD-O-3).[18] Patients with SCLC (ICD-0-3 histology code 804.1) of the lung (ICD-0-3 site code c34.0-c34.9) treated from 1988 to 2004 were analyzed.

Patients with stage I disease were selected. Although SEER does not provide chemotherapy details, it is assumed that almost all these patients received systemic therapy given small cell histology.

Overall and Cause-Specific Survival

Survival curves were generated by the method of Kaplan-Meier. Overall survival (OS) and cause-specific survivals were analyzed using Cox regression. Cause-specific and OS curves included patients with less than 4 months of survival. However, when performing a Cox proportional hazards analysis for the risk of death, to account for perioperative death in the analysis of postoperative adjuvant radiation therapy (RT) versus no adjuvant RT, regression was performed with patients with less than 4 months survival excluded. Central nervous system (CNS) brain radiation was reported as delivered in 32 patients (2%), recommended but unknown if administered in two patients (0.1%), not given in 438 patients (28%), and unknown in 1088 patients (70%). Because of the large unknown reporting of CNS radiation, and the possibility that those patients who were recorded as not having undergone CNS radiation actually received CNS radiation after the SEER registry window of data collection (within 4–6 months of diagnosis), CNS radiation was not included as a variable for analysis.

All statistical analysis was performed with STATA/SE 9.2 (Stata Corporation, College Station, TX).

RESULTS

A total of 1560 patients were identified as having stage I SCLC (Table 1). Age range was 27 to 94 years, with a median of 70 years, and 795 patients (51%) were men.

Most patients (1161, 74.4%) did not undergo any cancer-directed surgery. One hundred twenty-one patients (7.8%) underwent a surgical excision less extensive than a lobectomy (which included laser destruction, local tumor destruction not specified, wedge resection, segmentectomy, resection not otherwise specified, and local excision), 10 patients (0.6%) underwent pneumonectomy, and surgery was unknown for 21 (1.3%).

TABLE 1. Patient Characteristics—All Patients (n = 1560)

Gender	
Male	795 (51.0%)
Female	765 (49.0%)
Race	
White	1342 (86.0%)
Black	139 (8.9%)
Asian/Pacific Islander	67 (4.3%)
American Indian/Alaska Native/unknown	12 (0.8%)
Surgery	
No surgery	1161 (74.4%)
Local excision, tumor destruction, wedge resection, segmental resection	121 (7.8%)
Lobectomy	247 (15.8%)
Pneumonectomy	10 (0.6%)
Unknown whether surgery performed or type of surgery performed	21 (1.35%)
Radiation use	
No radiation	797 (51.1%)
External beam radiation	713 (45.7%)
Radioisotope and/or brachytherapy implant	7 (0.4%)
Unknown whether radiation delivered or unknown type of radiation	43 (2.8%)

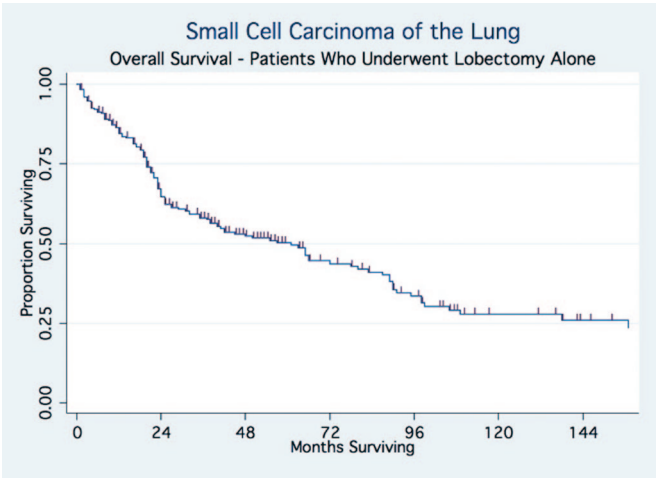

FIGURE 1. Kaplan-Meier curve for overall survival (lobectomy alone, node negative).

A total of 247 patients (15.8%) underwent lobectomy. Of the patients who underwent lobectomy, the age range was 40 to 89 years with a median age of 68 years, and 126 (51%) were men. Of the 247 patients who underwent lobectomy, 205 patients (83%) did not receive chest RT, 38 (15%) did receive external beam RT, and use of RT was unknown in 4 (1.6%).

For all patients who had a lobectomy regardless of radiation use, 3- and 5-year OS was 58% (95% confidence interval [CI] 51–64%) and 50% (95% CI 43–57%), respectively (Figure 1, Table 2). For patients who had a lobectomy and were not recorded as receiving adjuvant radiation, 3- and 5-year OS was 57.1% (95% CI 49.4–64.1%) and 49.1% (95% CI 41.2–56.6%), respectively. For patients who had a lobectomy

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TABLE 2. 3- and 5-yr Overall Survival, Lung Cancer-Specific Survival, and Noncancer Survival, Calculated by the Method of Kaplan and Meier

	Overall Survival		Lung Cancer-Specific Survival		Noncancer-Specific Survival	
	3-yr OS (95% CI)	5-yr OS (95% CI)	3-yr LCSS (95% CI)	5-yr LCSS (95% CI)	3-yr NCSS (95% CI)	5-yr NCSS (95% CI)
All patients (n = 1560)	31.0% (28.4–33.6%)	21.1% (18.7–23.6%)	38.5% (35.6–41.3%)	30.7% (27.7–33.8%)	84.8% (81.9–87.3%)	75.4% (71.1–79.3%)
All lobectomy (n = 247)	58.1% (51.1–64.5%)	50.3% (43.1–57.1%)	67.2% (60.0–73.3%)	64.3% (57.0–70.1%)	89.2% (83.5–93.0%)	82.6% (75.1–88.0%)
Lobectomy without external beam radiation (n = 205)	57.1% (49.4–64.1%)	49.1% (41.2–56.6%)	67.0% (59.2–73.7%)	64.4% (55.3–70.6%)	87.6% (81.0–92.0%)	82.1% (73.9–87.9%)
Lobectomy and external beam radiation (n = 38)	64.9% (45.5–78.9%)	57.1% (37.4–72.7%)	70.9% (51.2–83.8%)	[a]	96.1% (75.7–99.4%)	84.6% (58.4–94.9%)
Pneumonectomy (n = 10)	45.7% (14.3–73.0%)	[a]	45.7% (14.3–73.0%)	[a]	[b]	[b]
External beam radiation alone (n = 636)	28.4% (24.5–32.5%)	14.9% (11.4–18.9%)	35.3% (30.8–39.8%)	24.0% (19.1–29.1%)	84.6% (79.8–88.3%)	69.9% (60.8–77.2%)

[a] No further events. 5 yr numbers are the same as 3 yr.
[b] No noncancer deaths seen.
OS, overall survival; LCSS, lung cancer-specific survival; CI, confidence interval.

and did receive radiation, 3- and 5-year OS was 64.9% (95% CI 45.5–78.9%) and 57.1% (95% CI 37.4–72.7%), respectively. The use of radiation after lobectomy was not significantly associated with an increased survival compared with lobectomy alone (p = 0.90). This was not changed when excluding patients with less than 4 months of follow-up (to adjust for the bias of perioperative death) (p = 0.66).

For those patients who had a pneumonectomy (n = 10), 3- and 5-year OS were both 46% (95% CI 14–73%) with wide CIs because of the small number of patients. For the 121 patients with local excision, tumor destruction, wedge resection, or segmentectomy, 3- and 5-year OS was 47.9% (95% CI 38.8–57.3%) and 33.7% (95% CI 24.0–43.7%), respectively.

There were 1085 deaths in follow-up with 885 cancer deaths, of which 720 were attributed to lung cancer. There were 200 noncancer deaths. Lung cancer-specific and noncancer-specific survivals are listed in Table 2. The Kaplan-Meier curve for lung cancer-specific survival is shown in Figure 2. The use of radiation after lobectomy was not associated with an improvement in lung cancer-specific death (p = 0.71). This was also not changed when excluding patients with less than 4 months of follow-up (p = 0.95). The same can be said for noncancer-specific death (p = 0.74 and p = 0.34).

Four hundred seventy-five patients were alive at last follow-up. Median follow-up for patients alive was 22 months. The longest surviving patient was alive at 198 months after diagnosis.

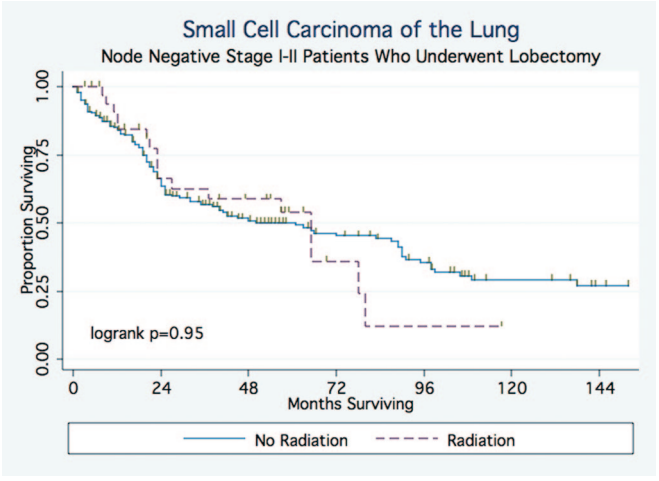

FIGURE 2. Kaplan-Meier curve for lung cancer-specific survival (lobectomy alone, node negative).

DISCUSSION

Based on our analysis of the SEER database, surgery without RT seems to offer reasonable survival in a cohort of patients who undergo lobectomy and who are node negative. Our study is limited by several important factors.

There are several unknown details regarding the intent and method of RT. The selection bias in choosing patients for radiation and/or surgery is unknown. Margin status, comorbidity, and indications for the use of radiotherapy are also unknown. For example, if patients who received radiation were more likely to have positive margins on resection, then this theoretically would have biased our study against radiation. Alternately, if patients with significant comorbid diseases were less likely to be referred for RT, this theoretically would have biased our study in favor of radiation. Specific

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details regarding fields, dose, and intent of radiotherapy are also not available in SEER. Radiation given to large radiotherapy fields with elective mediastinal irradiation concurrent with chemotherapy would be coded the same as an aborted course of limited radiation to gross residual disease.

In addition, whether patients did or did not receive chemotherapy is an important issue, although it is likely that most patients did receive chemotherapy because its use is the current standard of care in this chemoresponsive disease. Another unknown is the extent to which imaging studies were used to stage patients. Whether patients who underwent surgery were more likely to have undergone more extensive staging is unknown. Finally, there was no central pathology review. However, SEER registry identification of SCLC has high sensitivity (94.1%) and percent exact agreement (98%) in independent review.[19]

Finally, limiting the clinical applicability of this study is the fact that many of the identified patients were likely treated with surgery without the knowledge that the tumors were of small cell histology. In studies involving surgery as the primary treatment, approximately half of the patients were not diagnosed with SCLC preoperatively.[20] The SEER data does not provide this information, but it is likely that many of the patients were similarly not suspected to have SCLC until after a resection. In addition, patients in the SEER database were staged based on all available information, including pretreatment clinical findings, and also surgical pathology specimens. For thoracic sites, presurgical staging (versus postsurgical) was not available. This perhaps has caused our results to be more favorable, because those patients with clinical stage I disease who subsequently had more extensive disease found at surgery would not be included in our analysis group and would be upstaged by the SEER registrars.

Despite above limitations, the findings of this study are consistent with previous retrospective studies[8–13] and modern prospective trials[21] that seem to indicate that patients who are able to undergo resection for localized disease have improved OS compared with those who are unable to undergo resection. The average 5-year survival reported in other series for stage I SCLC after resection is 52% (range 37–76%),[8,10,11,14,22–24] which is quite comparable with the SEER data. The Veterans Administration Surgical Oncology Group reported on 148 patients who underwent a potentially "curative" resection, and noted that resection was definitely indicated in patients with T1N0 disease, with a 5-year survival rate of 59.9%.[14] A prospective multimodality trial showed a 100% local control rate in patients who had neoadjuvant chemotherapy (cisplatin/etoposide) followed by surgery in initially localized disease.[21] However, as noted previously, the only modern randomized trial that we are aware of comparing surgery followed by radiotherapy to radiotherapy after induction chemotherapy did not support the use of surgery.[15]

The variability in the reported results of other studies is likely due to differences in selection (proportion of incidental SCLC, size, extent of staging, etc.). It must be emphasized that "resectable" SCLC represents only a small proportion of patients with SCLC, which tends to magnify the effects of selection. Other studies have also shown that only about 10% of all patients with SCLC have been included in studies using primary surgical treatment (all stages, but mostly I and II).[24–26] This is compatible with our analysis of the SEER data, where we found that only 16.5% of patients with stage I cancer underwent lobectomy (15.8%) or pneumonectomy (0.6%).

This study reports data on more than 1500 patients, and represents national practice patterns and outcomes, and thus provides further insight into the role of surgery. Based on our analysis, surgery does seem to have a role in the treatment of localized disease, although this should be the subject of continued clinical study and randomized clinical trials.

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