Surgery for Early-Stage Small Cell Lung Cancer

Bryan J. Schneider, MD; Ashish Saxena, MD; and Robert J. Downey, MD; New York, New York

Key Words
Small cell lung cancer, surgery, resection, multimodality therapy

Abstract
Limited-stage small cell lung cancer remains one of the more frustrating malignancies to treat. Current standard of care typically includes platinum-based chemotherapy with thoracic radiation, and although response to therapy is high, most patients will ultimately experience relapse and die of recurrent disease. No high-level data exist supporting surgical resection of early-stage disease; however, several retrospective reviews and small single-arm studies suggest surgery may benefit patients with very limited extent of disease. This article reviews the available literature, and proposes guidelines for including potentially curative resection in the management of patients with limited-stage small cell lung cancer. (JNCCN 2011;9:1132–1139)

The American Cancer Society estimates that 222,500 new cases of lung cancer occurred in the United States in 2010. Of these, small cell lung cancer (SCLC) constitutes approximately 14%, or approximately 30,000 new cases annually. SCLC is characterized by a rapid doubling time and early development of lymph node and distant metastases, often already present at diagnosis. SCLC is also highly sensitive to chemotherapy and radiotherapy, making these treatment modalities the commonly accepted standard of care. Although the response rate to initial chemotherapy with or without radiation is high, most responses are not durable and more-effective treatments are desperately needed for this disease.

The Veterans Administration Lung Cancer Study Group (VALCSG) staging system defines limited-stage SCLC (LS-SCLC) as disease confined to one side of the chest according to scanning, or the ability of a radiation oncologist to encompass the disease in a “tolerable radiation field.” Patients who demonstrate SCLC on both sides of the chest or outside the thorax were classified as having extensive-stage SCLC. Approximately one-third of patients present with LS-SCLC, and the 5-year survival rate is between 13% and 38%. More recently, SCLC was also staged according to the TNM system, which is more descriptive, because TNM stages I through IIIA would all be classified as simply LS-SCLC by the VALCSG system. In 2007, the International Association for the Study of Lung Cancer, Lung Cancer Staging Committee recommended that the TNM staging system be used to stage SCLC in both routine practice and clinical trial design.

The standard treatment for LS-SCLC is definitive chemoradiation therapy without surgery; however, whether surgery has a role in patients with LS-SCLC has not been clearly examined. This article examines recent studies that suggest a benefit to adding surgical resection to other treatment modalities in selected patients with LS-SCLC.

History of Surgery for SCLC
During the 1950s and 1960s, surgical resection was the predominant treatment for SCLC. However, in 1969 the United Kingdom Medical Research Council reported the results of a randomized study of surgical resection versus thoracic radiation therapy for LS-SCLC with 5-year follow-up. This study randomized 144 patients...
with newly diagnosed operable SCLC to either pneumonectomy with lymph node dissection or thoracic radiation. Only approximately half of the patients assigned to the surgery arm underwent a complete resection, because the remaining patients underwent an exploratory thoracotomy alone or never received surgery. In contrast, 85% of the patients randomized to the radiation arm completedcurative treatment, with the remainder undergoing either palliative radiation or no therapy. The 3-year overall survival rate was 1% with surgical resection and 4% with thoracic radiation, even though most of the patients in the surgery group (62%) underwent subsequent radiation or chemotherapy. In contrast, approximately one-third of the patients in the thoracic radiation group underwent additional treatment. The 10-year follow-up data were subsequently published and showed a survival rate of zero with resection compared with 4% with radiation. The intent-to-treat analysis is justified; however, a substantial number of patients in the surgery arm never underwent surgery, and proponents of surgery have questioned whether a survival benefit may have been detected if more patients had actually undergone a complete resection. Nevertheless, the trial suggested a modest but durable response to thoracic radiation, and the use of surgery as standard therapy for LS-SCLC was largely abandoned.

Prospective Randomized Investigations

Early pilot studies evaluating induction chemotherapy followed by surgical resection for LS-SCLC touted promising 5-year survival rates of up to 36%. Subsequently, a multicenter, randomized trial was conducted to validate these early findings. More than 300 patients with LS-SCLC were initially treated with 5 cycles of cyclophosphamide, doxorubicin, and vincristine (CAV). An objective response was identified in 217 patients, and 146 were then randomized to either thoracotomy followed by thoracic radiation (n = 70) or thoracic radiation alone (n = 76). The goal of surgery was to remove the primary tumor and gross mediastinal disease, as defined by the investigators. All patients subsequently underwent prophylactic cranial irradiation (PCI). Unfortunately, no improvement in survival was identified with the addition of surgery to induction chemotherapy and adjuvant radiation, despite a complete resection rate of 77%. The median overall survival was 15 months with trimodality therapy versus 19 months with chemotherapy and radiation alone (P = .78). In addition, no improvement in local tumor control followed surgery. Patients with earlier-stage disease both at presentation and after thoracotomy did not seem to have an improved survival with surgery compared with those with more-advanced disease. However, patients with a peripheral solitary pulmonary nodule (T1N0M0) were specifically excluded, because bronchoscopic biopsy was used for diagnosis. Since this intergroup study was published in 1994, no prospective, randomized, controlled trials of surgery in LS-SCLC have been completed.

Prospective Nonrandomized Phase II Studies

Given the paucity of patients who present with potentially resectable SCLC, it is not surprising that investigators have focused on conducting small single-arm phase II studies to evaluate the potential clinical benefit of induction chemotherapy followed by surgical resection. In addition, several retrospective reviews of institutional data, and analyses of national cancer databases, together with prospective nonrandomized studies, suggest that surgery may improve survival in carefully selected patients with LS-SCLC.

Fujimori et al. treated 22 patients with LS-SCLC with 2 to 4 cycles of cisplatin, etoposide, and doxorubicin before performing surgical resection (mainly lobectomy with mediastinal lymph node dissection) and administering adjuvant cisplatin, etoposide, with or without doxorubicin. The 3-year overall survival rates for all patients, those with stage I/II disease, and those with stage IIIA disease were 67%, 73%, and 43%, respectively. In contrast to the Intergroup trial, 68% of the patients presented with clinical stage I or II disease. In addition, patients received platinum-based chemotherapy more similar to the regimens commonly used today. However, comparisons with the Intergroup study are difficult because the Fujimori study was much smaller and did not have a comparison arm of patients who received chemoradiotherapy alone.

Eberhardt et al. reported another prospective trial of surgical resection after induction therapy for LS-SCLC, in which 46 patients were assigned to...
Eight patients with stage IB/IIA disease received 4 cycles of etoposide and cisplatin (EP), and 22 patients with stage IIB/IIIA disease received 3 cycles of EP followed by a fourth cycle of EP plus concurrent hyperfractionated thoracic radiation (TRT) to a total dose of 45 Gy. After completion of induction therapy and repeat mediastinoscopy, patients without mediastinal lymph node involvement were eligible for surgical resection. The study also included 16 patients with stage IIIB disease who received definitive chemotherapy plus TRT to a total dose of 50 to 60 Gy. Of the 32 patients assigned to surgical resection, 23 experienced a complete resection. The 5- and 10-year overall survival rates for all patients were 39% and 35%, respectively, whereas the 5- and 10-year overall survival rates for the patients with initial IIB/IIIA disease were 44% and 41%, respectively (the overall survival rate for the 8 patients with stage IB/IIA was not reported). Although the survival rates were intriguing, the study was small, and the heterogeneous treatment based on the initial stage or response to induction therapy limited conclusions about the survival benefit of surgery added to chemotherapy and TRT.

Other studies have investigated the role of surgical resection for newly diagnosed LS-SCLC followed by adjuvant chemotherapy. The Japan Clinical Oncology Lung Cancer Study Group evaluated 61 patients with LS-SCLC from 17 centers: 44 had treatment based on their TNM stage from initial imaging plus mediastinoscopy. Eight patients with stage IB/IIA disease received 4 cycles of etoposide and cisplatin (EP), and 22 patients with stage IIB/IIIA disease received 3 cycles of EP followed by a fourth cycle of EP plus concurrent hyperfractionated thoracic radiation (TRT) to a total dose of 45 Gy. After completion of induction therapy and repeat mediastinoscopy, patients without mediastinal lymph node involvement were eligible for surgical resection. The study also included 16 patients with stage IIB disease who received definitive chemotherapy plus TRT to a total dose of 50 to 60 Gy. Of the 32 patients assigned to surgical resection, 23 experienced a complete resection. The 5- and 10-year overall survival rates for all patients were 39% and 35%, respectively, whereas the 5- and 10-year overall survival rates for the patients with initial IIB/IIIA disease were 44% and 41%, respectively (the overall survival rate for the 8 patients with stage IB/IIA was not reported). Although the survival rates were intriguing, the study was small, and the heterogeneous treatment based on the initial stage or response to induction therapy limited conclusions about the survival benefit of surgery added to chemotherapy and TRT.

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Abbreviations: A, doxorubicin; C, chemotherapy; CAV, cyclophosphamide, doxorubicin, vincristine; CCRT, chemoradiation; EP, etoposide platinum; LS, limited stage; MS, median survival; NR, not reported; PCI, prophylactic cranial irradiation; S, surgery; TRT, thoracic radiation.

*3-year survival.
†2-year survival.
clinical stage I disease, 9 had stage II disease, and 8 had stage IIIA disease at enrollment. Patients underwent an initial surgical resection with hilar/mediastinal lymph node dissection followed by 4 cycles of EP. None received postoperative TRT or PCI. Based on the initial clinical stage, the study showed overall 5-year survival rates of 66%, 56%, and 13% for stage I, II, and III, respectively.

Institutional Retrospective Reviews
Several retrospective reviews of institutional data also suggest surgical resection may enhance the outcome of patients with early-stage SCLC. In 1982, Shields et al. reviewed 132 patients who underwent potentially curative resection for SCLC followed by adjuvant chemotherapy. The 5-year survival rates were 23% for the entire cohort, 60% for patients with T1N0M0 disease, 30% for T1N1M0 or T2N0M0 disease, and less than 10% for T2N1M0 disease or greater. Although the survival for patients with larger tumors and regional lymph node involvement was comparable to that with conventional treatment without surgery, the impressive survival rate for patients with stage IA disease suggested that the addition of surgery may improve survival for patients in this category.

Granetzny et al. retrospectively analyzed data from 95 patients with TNM stage I through IIIB SCLC who underwent surgical resection as part of a trimodality treatment regimen. The first cohort of patients had clinical stage I to II disease and underwent surgical resection as initial treatment followed by adjuvant chemotherapy, TRT to 45 Gy, and PCI (group I). The second cohort of patients had stage III disease and underwent neoadjuvant chemotherapy before surgical resection, followed by adjuvant chemotherapy, TRT to 45 Gy, and PCI (group II). After surgical resection, this cohort was further subdivided into those who had a pathologic complete nodal response after induction chemotherapy (group IIA) and those who showed persistent nodal disease (group IIB). The patients in groups I and IIA had a median survival of approximately 31 months, whereas the median survival in group IIB was approximately 12 months. This study suggested a favorable survival with trimodality therapy in carefully selected patients who present without mediastinal lymph node involvement or who are downstaged with induction therapy. However, without a control arm of patients treated with definitive chemoradiation alone, the absolute improvement in survival attributable to the addition of surgery remains unknown.

Lim et al. retrospectively reviewed 59 patients with stage I through IIIB SCLC who had a complete resection with nodal dissection between 1980 and 2006. The overall 5-year survival rate was 52% and no statistically significant difference in survival was identified based on the clinical stage at presentation or pathologic stage after resection. Although the authors suggested that selected patients demonstrating locally advanced SCLC may benefit from complete tumor resection with nodal dissection, this study has several weaknesses. Complete information regarding subsequent therapy received by these patients was not available. In addition, the study was underpowered for reliable survival analysis and, like all retrospective reviews, likely prone to selection bias.

Brock et al. examined single-institution data on 82 patients with LS-SCLC who underwent surgery with curative intent. Of these patients, 41 underwent adjuvant chemotherapy, with a 5-year survival rate of 68% in patients treated with platinum-based chemotherapy compared with 32% in those treated with non–platinum-based chemotherapy (P = .04). For the subset of patients with resected stage I disease treated with adjuvant platinum- and non–platinum-based chemotherapy, the 5-year survival rates were 86% and 42%, respectively (P < .02). This study showed an impressive 5-year survival rate for patients with stage I SCLC treated with complete resection followed by adjuvant cisplatin-based chemotherapy without TRT, and suggested that adjuvant cisplatin-based therapy was superior to non–platinum-based regimens.

Finally, Bischof et al. retrospectively examined 39 patients with stage IA through IIIB SCLC who underwent surgical resection and lymph node dissection as initial treatment. Of these patients, 90% received adjuvant platinum-containing chemotherapy, 41% adjuvant TRT, and 54% PCI. The 5-year survival rate was 49% and a trend toward improved survival was seen among those who received adjuvant TRT compared with those who received surgery and chemotherapy alone (P = .07). The authors also found that the brain metastasis–free and overall survivals were significantly improved in those who received PCI (P = .01). They concluded that adjuvant
chemotherapy and PCI should be recommended for all patients who undergo surgery for LS-SCLC, and that thoracic irradiation should be included for patients with postoperative pathologic nodal metastatic disease.

**National Cancer Database Reviews**

Analyses of national cancer databases have been used to help define the role of surgery in LS-SCLC. Rostad et al.\(^2\) retrospectively reviewed the National Cancer Registry in Norway and examined data from 697 patients with LS-SCLC from 1993 to 1999. Among these patients, 180 were deemed to have stage I disease at presentation, with 111 believed to be potentially resectable but who received conventional chemotherapy or chemoradiation, 31 deemed not fit for surgery, and the remaining 38 underwent surgical resection as part of multimodality therapy. The 5-year survival rates were 45% (95% CI, 24%–66%) with surgery and 11% (95% CI, 4%–18%) with conventional therapy. Poor general health did not seem to explain the lower survival rate for the patients who did not undergo resection. The authors concluded that patients with clinical stage I SCLC should be strongly considered for surgical resection.

Yu et al.\(^2\) examined the National Cancer Institute SEER database and identified 1560 patients with stage I SCLC treated between 1988 and 2004. Approximately 200 patients underwent lobectomy and 38 received adjuvant TRT. The authors assumed (but, because of the limitation of the dataset, could not confirm) that most also received chemotherapy. The 5-year overall survival rates of patients with resected stage I SCLC with and without adjuvant TRT were 57% and 50%, respectively (\(P = .90\)). No improvement in cancer-specific death was identified with the addition of adjuvant TRT, and the authors concluded that lobectomy plus perioperative chemotherapy without TRT may offer reasonable overall survival for patients with node-negative (stage I) disease.

In a similar study that included patients with LS-SCLC higher than stage I, Schreiber et al.\(^2\) examined the SEER database for all patients diagnosed with LS-SCLC between 1988 and 2003. More than 14,000 patients were identified; 863 underwent surgical resection and 241 also received TRT. Of the almost 400 patients classified as localized disease (T1–2,N1–3,M0) who underwent surgical resection, approximately 45% were alive at 5 years, compared with 14% of the almost 2000 patients with localized disease treated with conventional therapy (\(P < .001\)). Patients classified as having regional disease (T3–4,Nx,M0 or T1–4,N1–2) who underwent surgery showed a 5-year overall survival rate of 26% compared with 9% among those treated with conventional therapy (\(P < .001\)). Although surgery seemed to benefit patients with more advanced LS-SCLC, a 5-year overall survival rate of 20% to 25% is commonly quoted for patients undergoing conventional chemotherapy and TRT without surgery.\(^2\)–\(^4\)

A subgroup analysis of the patients who received adjuvant TRT suggested that those with N0 and N1 disease did not benefit from the addition of radiation. The median survival for patients with resected N0 disease who received postoperative TRT was 41 months compared with 42 months for those who underwent surgery alone (\(P = .44\)). In contrast, patients with N2 disease who underwent postoperative TRT had a statistically significant improvement in survival, with a median survival of 22 months compared with 16 months for those who underwent surgery alone (\(P = .011\)). In addition, patients who underwent a lobectomy seemed to show an improvement in overall survival compared with those who had either a pneumonectomy or a sublobar resection. The extent of the procedure performed may reflect either the biology of the disease or the frailty of the patient, rather than morbidity inherent in the procedure itself. A pneumonectomy is associated with an increased operative mortality, but the need for this procedure implies more extensive disease (most likely hilar nodal metastases), which will negatively influence long-term survival.\(^2\) A sublobar resection may be performed because of surgeon preference in a patient with limited lung function, which itself is associated with a decreased long-term survival.

Although the data presented seem to support surgery for stage I SCLC, these results should be interpreted with caution given the inherent selection bias of any retrospective review. The SEER database does not provide data on patient performance status, the use of multimodality therapy (induction or adjuvant chemotherapy or radiotherapy), or the surgical margin status, all of which may influence patient survival. The International Association for the Study of Lung Cancer (IASLC) staging initiative reviewed
the survival data of 8088 patients with SCLC and complete TNM staging information. This analysis included a small cohort who underwent resection as part of therapy, but most data are from patients treated without surgery. Regardless of the treatment delivered, the 5-year survival rates for patients with clinical stage IA and IB disease were 38% and 21%, respectively. For those with pathologic staging available, the 5-year survival rates for stage IA and IB were 53% and 44%, respectively. Overall, the question remains whether patients with early-stage SCLC benefit from the inclusion of surgery in a multimodality therapy plan that involves modern staging technology, platinum-based chemotherapy, and advanced radiation techniques that can deliver high radiation doses more safely.

**Indications for Surgery**

Based on the data available, clinical scenarios exist in which surgery may be incorporated into the treatment of LS-SCLC. Specific case scenarios are illustrated below.

**Pathologic T1 to T2N0 Disease**

If the diagnosis of SCLC is made through needle biopsy of a solitary lung lesion and LS disease is suggested on the initial thoracic CT scan, a thorough investigation to rule out lymph node involvement and distant metastases should follow. This further testing should include PET imaging and a brain MRI (or CT with contrast if the patient is claustrophobic). Even in the presence of radiographically normal thoracic lymph nodes, pathologic mediastinal staging should be performed, which may include mediastinoscopy, mediastinotomy, endoscopic (bronchoscopic or esophageoscopic) with ultrasonographic-guided fine needle aspiration (FNA) procedures, thoracoscopy, or a combination of these procedures. After mediastinal staging, patients with clinical stage T1–T2,N0,M0 disease who are good surgical candidates may undergo resection of the tumor along with mediastinal lymph node dissection, with the goal of improving local control of disease and possibly overall survival. At surgical exploration, a mediastinal nodal resection is performed first, with frozen section histologic analysis. If nodes are negative or if involved nodes are found intraoperatively but all disease appears able to be resected with a lobectomy/bilobectomy, then it is reasonable to proceed with resection. Pneumonectomy for nodal disease seems likely to be of severely limited or no benefit.

Surgeons commonly perform exploratory thoracotomies for indeterminate lung nodules, and the diagnosis of SCLC can be made intraoperatively. Again, a mediastinal nodal resection should be performed first with frozen section histologic analysis, and if negative, or if involved nodes are found intraoperatively but all disease appears resectable with a lobectomy/bilobectomy, then resection is reasonable. Adjuvant EP for 4 cycles is recommended and should include concurrent mediastinal radiation if node-positive disease is identified on postoperative pathologic review.

**Solitary Peripheral Nodules**

Because fewer than 5% of SCLC cases present as a solitary peripheral nodule, a diagnosis of SCLC using CT-guided FNA should be viewed with suspicion. This is particularly true in nonsmokers who have a vanishingly small probability of developing SCLC. Given the spectrum of neuroendocrine tumors and the known difficulties in differentiating them based on scant tissue from an FNA, a nodule considered to be a small cell carcinoma based on FNA may in fact be a carcinoid or, less commonly, a large-cell neuroendocrine carcinoma. Resection of a lesion that has no evidence suggesting locoregional disease or has distant evidence suggesting metastatic disease and that persists after appropriate chemoradiotherapy for small cell carcinoma is reasonable to rule out an error in cytologic diagnosis.

**Mixed Histology Tumors**

Tumors may be mixed small cell/large cell carcinoma; however, only the small cell component may be diagnosed on an FNA or nodal biopsy. Mixed histology may be suspected clinically if the tumor initially responds to chemoradiotherapy appropriate for small cell carcinoma but then has recurrence at the primary site of disease. It is reasonable to offer surgical resection to these patients with the goal of treating the non–small cell lung cancer component of the disease.

**Conclusions**

Whether a role exists for surgery in the management of LS-SCLC remains controversial. Current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Small Cell Lung Cancer recom-
mend surgery only as an initial treatment option in patients who present with T1–T2,N0,M0 (stage I) disease confirmed with pathologic mediastinal staging (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). In these patients, lobectomy with a mediastinal lymph node dissection is considered reasonable. If postoperative pathologic staging shows no involved lymph nodes, adjuvant chemotherapy alone with EP is recommended, although carboplatin/etoposide is also an option. If involved hilar or mediastinal lymph nodes are identified, then adjuvant chemotherapy with concurrent mediastinal radiation is recommended; several different regimens are recommended in the NCCN Guidelines. In both cases, prophylactic cranial irradiation is advised to decrease the risk of brain metastases and improve overall survival. Other commonly accepted indications for surgical resection in SCLC include solitary peripheral nodules diagnosed as small cell carcinoma intraoperatively, and mixed-histology tumors showing progression of the non–small cell component after treatment with chemoradiation therapy appropriate for small cell carcinoma. The authors acknowledge that these recommendations represent consensus opinions based on low-level evidence largely consisting of retrospective reviews and nonrandomized phase II trials. Regrettably, there is a clear lack of prospective, randomized, controlled trials investigating the benefit of surgery in the multimodality treatment of LS-SCLC. Ideally, an international, prospective, randomized trial investigating current multimodality therapy with and without surgery would be supported by the thoracic oncology community. This would allow timely accrual, hopefully clarify the use of surgical resection, and thereby further refine the treatment approach for LS-SCLC.

References

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