Surgery in the Management of Small Cell Lung Cancer

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Key Words

Small cell lung cancer, surgery, metastases, thoracic surgery, pulmonary carcinoma

Abstract

Because most patients with small cell cancer of the lung present with distant metastatic disease, the treatment is almost always medical therapies without surgery. However, a small number of patients present with resectable disease, and this review summarizes the available literature addressing the possible role for surgery in the treatment of these patients. (*JNCCN* 2004;2:159–162)

Resection with curative intent is rarely possible in patients with small cell lung cancer (SCLC), because most patients present with either diffuse locoregional disease or distant metastases. Chemotherapy, which is well known to induce dramatic responses, is the mainstay of treatment for this disease. The addition of thoracic radiation therapy can improve local control and survival over chemotherapy alone for patients with limited stage disease. However, it is possible that (rarely) surgery may benefit SCLC patients. This review discusses the relevant literature on this subject. We must emphasize that clinical trials exploring the role of surgery in SCLC are difficult to conduct because of the rarity of resectable disease. As a result, the evidence available is often both based on small groups of patients and retrospective, and therefore, any advantage attributed to surgery in these studies must be considered unproven. Multiple comprehensive reviews on this topic are available for the reader desiring additional details or viewpoints.[1–5]

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Review of the Literature

The preferred treatment for SCLC before 1973 was surgical excision. However, a review from Memorial Sloan-Kettering Cancer Center at that time suggested that only a fraction (7%) of patients presented with resectable disease, and prolonged survival was rare.[6] In a similar series from M. D. Anderson Cancer Center,[7] the median survival of SCLC patients without known metastases was 5 months when treated surgically, and the longest survivor lived 39 months. These results were no better than those achieved historically by medical therapy alone. In a 1973 report summarizing the 10-year results of a British Medical Research Council (BMRC) study that randomized patients to receive either surgery alone (n = 71) or radiation therapy alone (n = 73), the authors found that "…radical radiotherapy has a somewhat better result than surgery in patients with SCLC."[8] This study has been criticized by some[9] as being limited in that (1) disease had to be central (i.e., could be biopsied with a rigid bronchoscope), (2) no intraoperative staging was performed, and (3) only about half of the patients underwent complete resections. The study can be further faulted for not using modern imaging for staging. However, this study changed clinical practice in that resections were largely abandoned in favor of radiation therapy. Soon thereafter, effective chemotherapy was incorporated into the management of SCLC.

Since then, only a few studies have described patients with SCLC treated with surgery alone.[10–12] One of these studies[12] compared patients managed with surgery alone with those who received chemotherapy after resection, and the results are instructive. Stage I patients treated with surgery alone had a 5-year survival of 12%, but patients treated with surgery and postoperative chemotherapy had a 5-year survival rate of 61%. Given the limitations of the BMRC study, the subsequently published studies hold open the possibility that surgery may benefit a small group of patients.

Two large studies address surgery with adjuvant chemotherapy. The first, from the University of Toronto,[13] retrospectively described 77 patients with early stage SCLC treated initially by resection. Sixty-three patients subsequently received combination chemotherapy, 49 prophylactic cranial irradiation, and 35 received thoracic radiation. The overall 5-year survival was 31%, but this was strongly associated with stage. Stage I patients had a 5-year survival of 48%; stage II, 25%; and stage III, 24%. A later article from the same group suggested that surgery followed by chemotherapy had the same outcome as treatment in the reverse order.[14]

The second study of adjuvant therapy was a prospective trial by The Lung Cancer Study Group of the International Society of Chemotherapy, which enrolled 183 patients with stage I (T1-2, N0) SCLC.[15] After surgery, patients were randomized to receive standard chemotherapy with cyclophosphamide, doxorubicin, and vincristine, or sequential therapy with 3 different chemotherapy regimens. Thoracic radiation was not used, although patients with no evidence of disease were offered prophylactic cranial irradiation. The 30-month survival for N0 patients was 63% and for N2 patients was 37%.

Several small retrospective and nonrandomized prospective studies showed the feasibility of treating patients with limited stage SCLC with induction therapy followed by surgery.[16–19] As with the studies of surgery and adjuvant therapy, survival strongly corresponds with stage. In particular, patients with residual mediastinal disease fare poorly, suggesting a role for pre-resection mediastinoscopy.[20]

Although the benefit of combined chemoradiation for limited stage SCLC has been firmly established, a meta-analysis evaluating the role of thoracic radiotherapy[21] found the local recurrence rate to be 35% to 50%, which is where it has remained even with intensified radiation fractionation.[22] This local failure rate has led to intermittent reconsideration of surgery as a better means of obtaining local control.

The only available prospective randomized study that addresses the relative effectiveness of surgery and radiation therapy was performed through the Lung Cancer Study Group.[23] In that study, 328 patients with node-positive SCLC were enrolled; 146 responding patients were randomized to either surgery followed by thoracic radiation or radiation alone. Local failure rates and survival in the two groups were similar. However, this trial can be criticized for not using cisplatin-based chemotherapy or concurrent thoracic radiotherapy, limiting the applicability of its conclusion to current theory, and for only 50% of the patients being randomized.

The relative advantages of surgery versus radiation for local control in patients with N0-N1 and in patients with N2 disease after induction chemotherapy are not clearly known. Several small retrospective and nonrandomized prospective studies have evaluated patients with stage I-IIIA disease treated with induction therapy and surgery. The most recent of these studies enrolled 22 patients, of which 21 responding patients underwent resection. The authors found a 3-year survival rate of 73% for N0 and N1 patients and 43% for N2 patients.[19] Retrospective data on SCLC treated with induction chemotherapy and surgery suggest that patients with mediastinal nodal disease fare worse if treated with surgery rather than radiation.[20]

Finally, another rationale supporting surgery after initial therapy is for tumors of mixed histology. The diagnosis of mixed SCLC-NSCLC is rare, occurring in approximately 1% of patients with newly diagnosed SCLC.[24] The NSCLC component may represent the residual tissue after the more chemosensitive SCLC has been eradicated. Of 28 specimens resected after chemotherapy in a University of Toronto series,[25] 18 had pure SCLC, 6 had pure NSCLC histology, and 4 were mixed in histology. In the Lung Cancer Study Group randomized trial of adjuvant surgery,[15] NSCLC or mixed SCLC and NSCLC represented 11% of the resected specimens. In the largest series available,[26] which describes 26 patients with mixed SCLC-NSCLC, the 5-year survival for patients with stage I disease was 31%, but for all other patients, it was 0%.

Practice Guidelines

Given the data reviewed, we suggest the following guidelines for surgery in patients with SCLC:

Solitary Pulmonary Nodules Identified Intraoperatively as SCLC

If during thoracotomy for an indeterminate pulmonary nodule, the diagnosis of small cell carcinoma is made, a mediastinal lymph node dissection should be performed with frozen section analysis of the nodes. If limited disease that can be encompassed surgically by a lobectomy or bilobectomy is found, resection is reasonable. Because pneumonectomy is associated with a significant surgical mortality and limits the reserve

of a patient who faces chemoradiotherapy, it will be only rarely appropriate.

Because presentation with resectable disease is common for histologies other than SCLC and uncommon for SCLC (occurring in only about 4% of SCLC patients[27]), this allows pathologic confirmation that the disease is actually SCLC and not another entity such as a carcinoid. Furthermore, it allows complete staging, which will have prognostic and treatment implications. Finally, it is possible that resection of SCLC may be associated with a better rate of locoregional control.

In general, our practice is to recommend postoperative chemotherapy for resected N0 small cell patients and postoperative chemoradiotherapy for patients with resected N1 or N2 disease. However, this is based on very little data.

Very Early Stage SCLC Recognized Preoperatively

Tumors diagnosed preoperatively as small cell carcinoma and that are clinically N0,M0 after a complete staging evaluation (including mediastinoscopy and possibly mediastinotomy) may be considered for surgical resection. Resection may reveal that the tumor is actually a carcinoid. Interoperative frozen section analysis of a complete hilar and mediastinal lymph node dissection is valuable; the presence of extensive nodal disease that would be difficult to encompass surgically would lead to consideration of aborting the resection. Postoperative chemotherapy is recommended for resected N0 small cell patients, and postoperative chemoradiotherapy is recommended for resected N1 or N2 patients (again, based on limited data).

Tumors diagnosed preoperatively as small cell carcinoma and that are clinically N1,M0 after a complete staging evaluation (including mediastinoscopy and possibly mediastinotomy) are generally treated initially with chemotherapy and radiation, and if restaging is negative for distant metastatic disease, considered for resection.

Tumors diagnosed preoperatively as small cell carcinoma and that are pathologically proven to be N2 by mediastinoscopy or mediastinotomy are generally treated with definitive chemoradiation therapy.

Growth in a Treated SCLC

Growth in a residual mass of medically treated SCLC may be considered for resection in that about 10% of such patients will have residual non-small cell carcinoma that will not be responsive to small cell chemotherapy or may have a carcinoid misdiagnosed as SCLC.[16,23,25]

New Mass After Treatment for SCLC

A mass arising in a separate area of the lung more than 2 years after treatment for SCLC should be evaluated for possibly being a second primary cancer, which is one of the common causes of death in survivors of SCLC.[28,29] If confirmed as a new primary, treatment should be according to standard principles for the management of lung cancer.

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