Thoracic Surgery in Early-Stage Small Cell Lung Cancer

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KEYWORDS

• Early stage • Small cell lung cancer • Surgical treatment

KEY POINTS

- Patients with limited stage small cell lung cancer, stage I (T1-T2, N0) should be offered surgery as part of their treatment plan.
- Lobectomy is the surgery of choice in patients who can tolerate the procedure.
- Surgery with chemotherapy should be used because this can increase 5-year survival.

INTRODUCTION: NATURE OF THE PROBLEM

In 2017, approximately 222,500 Americans will be diagnosed with lung cancer. From these new cases, 10%–15% will be small cell lung cancer (SCLC).[1] Since the origin of its name and description in 1926, SCLC has been difficult to treat because of its aggressive nature and significant rate of recurrence (50%–80%).[2–4] Before World War II, surgery was the initial treatment of choice in patients amenable to resection, whereas radiation therapy was reserved for those with unresectable disease. However, in the 1960s and 1970s, advancements in radiotherapy[5,6] and chemotherapy[7,8] were shown to have similar survival rates when compared with surgical management.

A recent review article by Haddadin and Perry[9] accurately divides the historical course of SCLC into 3 intervals: (1) the characterization of SCLC (1920s–1950s); (2) advancements in staging and treatment—chemotherapy and radiation (1960s–1980s); and (3) a dormant period during which advancements appear to have stalled (1990s–current). During this lull in therapeutic progress, questions have arisen about whether or not surgery is still a viable treatment option for early-stage SCLC. In this article, the authors discuss the current literature on treatment of early-stage SCLC and whether surgery should be considered a viable treatment modality.

THERAPEUTIC OPTIONS AND SURGICAL TECHNIQUES

Epidemiology

The American Cancer Society estimates the incidence of lung cancer to reach 222,500 in 2017.[1] In 1993, SCLC represented 25% of all lung cancers; today SCLC represents 10%–15%.[1,10] This significant decrease is thought to be attributed to downward trends in smoking, because the overall risk of developing SCLC has been related to the quantity and length of time a patient has smoked.[11]

Most patients with SCLC will present with metastases or extensive stage disease, rendering most disease not amenable to surgical resection. Only 4% to 12% of patients have solitary pulmonary nodules that can be classified as very early-stage disease.[12] Many think this is a result of the

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increased number of mutations involved in SCLC that involve downregulation of TP53 genes and histone modification.[13] Even patients with limited stage disease typically present with evidence of hilar, mediastinal, or supraclavicular nodal involvement, altering their clinical stage and negating their ability for resection.[14]

Staging of small cell lung cancer

Initially, the aggressive nature of SCLC earned its own staging system separate from the TNM staging system. The Veterans Administration Lung Cancer Study Group (VALSG) was the first to assign the designation of limited-stage (LS) and extensive stage (ES) disease. LS disease was defined as a tumor confined to 1 hemithorax, and primary tumor and regional lymph nodes encompassed in a safe radiation portal.[14] LS disease included left recurrent laryngeal nerve involvement, nonmalignant ipsilateral pleural effusions, and superior vena cava involvement. ES disease was defined as anything that could not be classified in this category.

In 1987, the International Association for the Study of Lung Cancer revised the VALSG system to adapt to the TNM staging system: LS disease included stages I to III and ES disease included stage IV.[15] The staging was again revised in 2007 in an effort to further stratify patients with LS disease.[16] The identification of subgroups of LS disease followed a retrospective study on 8000 patients with SCLC. This substantial review showed patients with mediastinal lymph node involvement (stage III) to have significantly worse 5-year survival than patients with N1 lymph node involvement (stage II) (13% vs 18%; $P = .003$).[16] The 5-year survival rate was also significantly different between patients with stage II and stage I disease (21% vs 38%; $P = .008$). The TNM system, however, is limited in that it requires mediastinal lymph node biopsies with pathology confirmation at the time of surgery; only 2% to 6% of patients with SCLC present at a stage that is amenable to surgical treatment.[14]

Both the VALSG and the TNM staging systems are used today. However, the National Comprehensive Cancer Network (NCCN) has provided formal definitions for LS and ES disease, as follows:

- LS: American Joint Committee on Cancer (AJCC) (7th edition) stage I to III (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3–4 due to multiple lung nodules or tumor/nodal volume too large to be encompassed in a tolerable radiation plan.
- ES: AJCC (7th edition) stage IV (T any, N any, M1a/b), or T3–4 due to multiple lung nodules or tumor/nodal volume too large to be encompassed in a tolerable radiation plan.[17]

Current overall 5-year survival rates for LS disease are 48% for stage I, 39% for stage II, and 15% for stage III, respectively.[18]

Small Cell Lung Cancer Treatment Options

In the 1950s, SCLC was designated as a separate entity from other types of lung cancer. As previously mentioned, surgery was the initial treatment modality for SCLC. However, in the late 1960s, the Medical Research Council demonstrated there to be no survival benefit at 5 years for patients who received surgery compared with those who received radiation therapy alone.[5] In fact, the patients who received radiation therapy alone were found to have an increased rate of survival at 2 years (10% vs 4%), 4 years (7% vs 3%), and 5 years (4% vs 1%).[5] This same group continued their research and published a 10-year follow-up study with similar results. They evaluated 144 patients with SCLC randomized to surgery (n = 71) and radiotherapy (n = 73).[6] There were no 10-year survivors in the surgery arm, but 3 patients remained in the radiotherapy arm. Following the statistically significant difference ($P = .04$) in mean survival between the surgery (199 days) and radiotherapy (330 days) treatment arms, radiation therapy replaced surgery as the preferred treatment modality for SCLC.

Over the next several decades (1960s–1980s), chemotherapy was also shown to be successful in treating SCLC. In 1962, Watson and Berg[7] demonstrated the benefit of nitrogen mustard in patients with SCLC. Several years later (1969), the Veterans Administration Hospitals evaluated cyclophosphamide, which also showed benefits in survival.[8] In 1984, Feld and colleagues[19] evaluated 153 patients with LS disease who were treated with chemotherapy (cyclophosphamide, doxorubicin, and vincristine), thoracic radiation, and prophylactic cranial irradiation. Approximately 52% of these patients achieved complete response.

In 1979, Sierocki and colleagues[20] revealed etoposide and cisplatin to be a viable treatment option (complete response rate: 52%). Since then, combination therapy with etoposide and cisplatin, along with radiotherapy, has remained the standard of care. During this exciting season of new chemotherapy agents, much promise was given for a possible cure, because SCLC continued to have good chemotherapeutic response. However, for the last 35 years, there has been a lull in