Neuroendocrine Tumors of the Lung

The Role of Surgery in Small Cell Lung Cancer

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KEYWORDS

• Staging • Indications • Surgery • Results • Small cell lung cancer

KEY POINTS

- The role of surgical treatment in the management of patients with small cell lung cancer (SCLC) remains controversial.
- Although in the past, 2 randomized studies have failed to show any benefit on survival by adding surgery to chemotherapy (CTx), different retrospective and prospective reports, including the recently published studies using the database of the Cancer Institute Surveillance Epidemiology and End Results, showed that surgery offers a reasonable overall survival in a subset of patients with stage I and II SCLC.
- Two important recommendations have been introduced concerning SCLC histology as a high-grade aggressive neuroendocrine tumor and the use of TNM classification in SCLC staging and in clinical trials.
- Patients' selection is fundamental, and it should include extensive radiologic staging and mediastinal lymph-node biopsy.
- The use of a positron emission tomography scan is likely to improve the accuracy of staging.
- Through primary surgery or after induction CTx, a complete tumor resection associated with systematic hilar/mediastinal lymphadenectomy should be achieved.
- Adjuvant CTx is also recommended in patients with stage I disease; prophylactic cranial irradiation prolongs survival in those patients who achieve a complete or partial response to initial treatment.
- Surgery can be performed with a curative intent in patients with stage I or II disease or significant nodal response after CTx.

INTRODUCTION

Small cell lung cancer (SCLC) represents a distinct pathologic and clinical entity, accounting for approximately 10% to 20% of all primary lung cancers, with incidence rates declining in men but continuing to increase in women in most countries.[1,2] SCLC is the most aggressive among lung cancer subtypes: it has a poor prognosis and is closely associated with smoking history. Regional lymph node involvement or distant metastasis is present in more than 90% of patients at the time of diagnosis.[3] The Veterans Administration Surgical Oncology Group (VASOG) has introduced a simple staging system to be used in their clinical trials, dividing SCLC into 2 disease subgroups termed *limited disease* (LD) and *extensive disease* (ED). LD-SCLC was defined as a disease that can

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potentially be encompassed within a tolerable radiation field. Tumor extension is limited to the hemithorax, including regional and ipsilateral supraclavicular nodes. ED-SCLC was classified as a disease outside of these confines.[4]

Two important recommendations have been introduced in the last decade concerning SCLC histology and its TNM classification: (1) In 1999, the World Health Organization's classification of lung and pleural tumors recognized SCLC as a high-grade, biologically aggressive neuroendocrine tumor with a different immunohistochemical and morphologic appearance, different from typical and atypical carcinoid, and large cell neuroendocrine carcinoma.[5] (2) In 2007, the International Association for Study of Lung Cancer (IASLC), using the IASLC database of 8088 SCLC cases, performed a survival analysis for clinically staged patients. Prognostic groups were compared, and the new IASLC TNM proposals were applied to this population and to the Surveillance, Epidemiology, and End Results (SEER) database. This analysis demonstrated the clinical TNM staging utility for this malignancy, so that TNM staging is now recommended for SCLC and stratification by stage I to IIIA should be incorporated in clinical trials or early disease.[6,7]

Surgery was the treatment choice of in the 1960s, but the reported cases showed a generally worse prognosis compared with other lung cancer subtypes.[8,9] The introduction of chemotherapy (CTx) and the results of a randomized study organized by the British Medical Research Council, published by Fox, highlighted the dogma that surgery alone is not the optimal treatment of patients with SCLC.[10] In this study, 144 patients were randomized: 71 to surgery and 73 to radiotherapy. The median survival time in the surgery group was 199 days versus 300 days in the radiotherapy one; the 5-year survival rates were 1.4% and 4.1%, respectively. Although the observation that radiotherapy was superior to surgery, the overall results of both arms seemed to be very poor. However, this study has been criticized for many reasons; the poor survival after surgery might be related to the fact that histologic diagnosis was based on results from rigid bronchoscopy, so that only patients with centrally located tumors were eligible for this study. Moreover, the patients were not staged using the modern technical standards (computed tomography scan, mediastinoscopy, 2-Fluor-2-desoxy-D-glucose (FDG)–positron emission tomography [PET], and so forth), and intraoperative staging was not complete because mediastinal lymph-nodal dissection was generally not performed.[11]

Systemic CTx was then introduced for the treatment of SCLC and resulted in objective response rates of 80%, palliation of symptoms, and prolonged survival.[12] Despite this, long-term survival remained disappointing: According to the initial disease extent, long-term survival rates did not exceed 10% to 15% in LD-SCLC. In 537 of such patients, who received various protocols of intensive CTx or chemoradiotherapy combination with complete clinical response, Elliott and colleagues[13] identified, at autopsy, a residual tumor at the primary site in 64% and in hilar and mediastinal lymph nodes in 53%.

Therefore, strategies to improve outcomes have included CTx concurrently with radiation or have tried intensification of radiotherapy as early as possible.

A major systemic risk for long-term SCLC survivors is the brain metastasis development. A careful meta-analysis of published randomized trials demonstrated a significant effect of prophylactic cranial irradiation (PCI) on survival in patients with LD and complete response.[14]

In 1989, the Toronto Lung Oncology Group published encouraging results with a prospective study of adjuvant surgical resection after CTx for LD-SCLC. They found that adjuvant surgical treatment significantly contributed to improved survival for patients with stage I disease (N0 tumors and tumors of mixed histology). They emphasized the importance of intensive preoperative staging, including mediastinoscopy for possible candidates to adjuvant surgery as definitive local treatment.[15]

To determine the role of surgery in combination with CTx and radiotherapy, with the aim to prolong survival and improve the cure rates, the Lung Cancer Study Group in cooperation with the Eastern Cooperative Oncology Group and the European Organization for Research and Treatment of Cancer started a prospective randomized trial of adjuvant surgical resection. Patients received 5 cycles of CTx with cyclophosphamide, doxorubicin, vincristine, and etoposide; in absence of toxicity or progressive disease, they were restaged and functionally evaluated for possible thoracotomy. Eligible patients were randomized, either to surgical resection followed by thoracic radiation and PCI or to radiotherapy and PCI without surgery. One hundred forty-four patients were randomized: 68 received surgery followed by radiotherapy and 76 radiotherapy alone. Only 54 out of the operated patients had a pathologic complete resection (R0). The median overall survival time was 14 months and 18 months for the randomized patients. There was no significant difference in median or overall survival between the two randomizations.[16] However, different aspects of this study have been criticized. Pathologic staging was available for the group of patients who