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Defining outcomes of patients with clinical stage I small cell lung cancer upstaged at surgery

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ABSTRACT

Background: A proportion of patients with clinical stage I small cell lung cancer (SCLC) will be upstaged following surgical resection. The existing data regarding the management of upstaged SCLC patients and guidelines for their treatment remains sparse. The primary objective was to describe the impact of pathologic upstaging following surgical resection.
Methods: The National Cancer Database was queried for patients with clinical stage I SCLC (cT1-2a,N0,M0) who underwent resection with curative intent followed by adjuvant therapy, excluding patients who underwent surgery alone. Clinical and pathologic T, N, and M staging were compared to identify patients that were upstaged.
Results: Four-hundred and seventy-seven patients were identified with clinical stage I SCLC. Pathologic upstaging occurred in 25% (117). Of those upstaged, 30% (35) were due to a higher pathologic T descriptor and 81% (95) were due to the presence of nodal disease. Overall 5-year survival was significantly worse for upstaged patients compared with those patients who remained a pathologically stage I (36% vs 52%, $p < 0.001$). Among patients with positive lymph node involvement, adjuvant chemotherapy and radiation therapy was associated a significantly improved 5-year survival compared to adjuvant chemotherapy alone (20% vs 55%, respectively, $p < 0.01$). The use of adjuvant chemotherapy and radiation therapy in patients with nodal disease after surgical resection was an independent predictor of improved survival (HR 0.36, 95% CI 0.18–0.73, $p < 0.01$).
Conclusions: Pathologic upstaging is common after surgical resection of stage I SCLC, and is associated with significantly inferior survival. These data provide evidence that recommend the use of adjuvant chemotherapy and radiation therapy in the setting of nodal upstaging after resection of clinical stage I SCLC patients.

1. Introduction

Small cell lung cancer (SCLC) is known for its rapid growth, early development of metastases, and poor prognosis [1]. Despite the aggressive nature of SCLC, a small proportion of patients are diagnosed with clinical stage IA/B disease (clinical T1-T2a, N0, M0; tumor no greater than 5 cm (T1-2a), no regional lymph node metastasis (N0), no distant metastasis (M0)). For this select group, recent evidence has demonstrated a role for upfront surgical resection and current guidelines recommend consideration of curative-intent surgery followed by platinum-based adjuvant chemotherapy [2–7]. Additionally, some series have found up to one-half of patients who undergo surgery for non-small cell lung cancer (NSCLC) may incidentally have SCLC and therefore may be treated with curative intent surgery [2].

Prior to curative-intent surgery, invasive mediastinal staging and extrathoracic imaging is recommended to evaluate for regional and distant disease. However, modern single-institution series demonstrates significant variability in the performance of preoperative staging, and consequently, pathologic upstaging following resection is a common occurrence [8–11]. To date, there are no large nationally representative data that identify the incidence of pathologic upstaging following surgical resection for SCLC. There are limited data regarding the clinical outcomes of patients who are pathologically upstaged due to nodal metastases, which is critical

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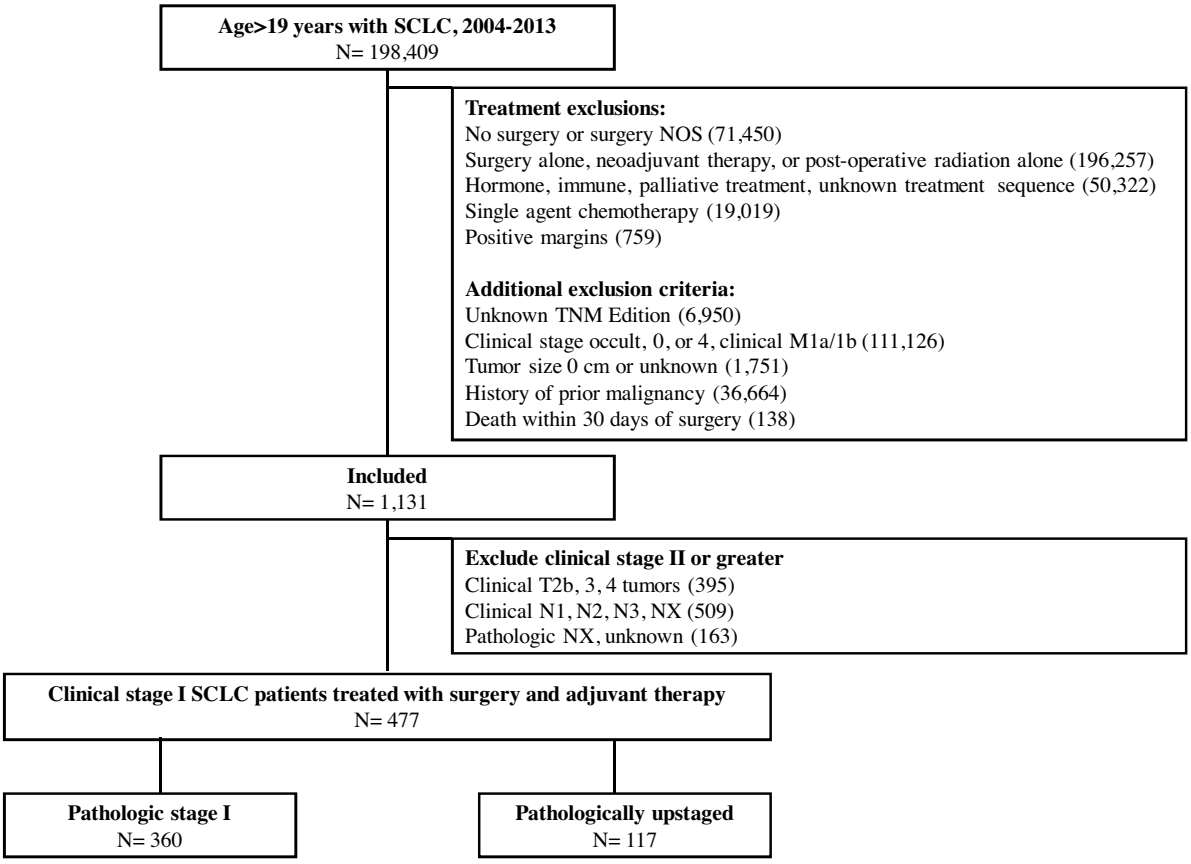

Fig 1. Study cohort exclusion criteria.

to define postoperative recommendations for adjuvant therapy [3]. Furthermore, in patients with nodal disease identified at the time of surgical resection, recommendations for the use of adjuvant radiation in addition to chemotherapy are based upon limited evidence [3].

The objective of this study was to describe the impact of pathologic upstaging after surgical resection in a cohort of clinical stage I SCLC patients. A secondary objective was to clarify the impact of adjuvant therapy in surgically resected patients pathologically upstaged due to the presence of nodal disease.

2. Material and methods

2.1. Data source

The National Cancer Database (NCDB) is a hospital-based tumor registry maintained as a joint effort of the American College of Surgeons and the American Cancer Society. This database captures approximately 1500 institutions with Commission on Cancer accreditation, including approximately 67% of all lung and airway malignancies in the United States [12]. The data used in the study are derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator. This study was granted exemption from the Yale University School of Medicine Institutional Review Board.

2.2. Study population

The NCDB Participant User Data File was queried to identify patients 20 years and older who underwent surgical resection for invasive SCLC, histology codes 8041-44/3, between 2004 and 2013. Patients with clinical stage I SCLC tumors (T1 or T2a, N0, M0 according to the American Joint Committee on Cancer classification 7th edition) were selected. Patient diagnosed in 2013 were included for purposes of describing the pathologic upstaging of patients after surgical resection, but were excluded from all survival analysis due to the lack of follow-up data. Fig. 1 demonstrates the exclusion criteria and patient selection. The total number of patients within the dataset that were excluded for a given criterion are displayed and the criteria are not mutually exclusive.

Patients identified as having clinical T2 classification without specific T2a/T2b designation, and also identified as clinical stage I, were assumed to be T2a and included, while patients recorded as T2b were excluded, methodology consistent with prior NCDB lung cancer studies [13]. Patients coded as clinical stage 0 or unknown stage were excluded, as were patients with unknown clinical nodal status, NX. Those with clinical or pathologic evidence of M1 disease were also excluded. Patients treated with no surgery or a surgical procedure not otherwise specified, a history of previous malignancy, management with single agent chemotherapy, or the use of experimental, immune, hormonal, or palliative therapy were excluded. Patients with positive surgical margins were excluded from the study to reduce the heterogeneity of the study population, despite these patient's increased likelihood of upstaging, as demonstrated in the NSCLC literature [13]. Tumors of unknown size, or a size documented as 0 cm, were excluded. Patients were stratified by treatment with adjuvant chemotherapy or adjuvant chemotherapy and radiation therapy. Patients who died within 30 days of surgery were excluded to avoid the impact of surgical morbidity on survival outcomes. Patients treated with surgery alone, without adjuvant treatment, were excluded from analysis as these patients would