Bolstering the Case for Lobectomy in Stages I, II, and IIIA Small-Cell Lung Cancer Using the National Cancer Data Base

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Introduction: Current therapy for small-cell lung cancer (SCLC) relies on chemoradiation therapy, and the role of primary surgical resection in these patients remains controversial. A minority of SCLC patients present without metastatic disease and are candidates for surgery. This study investigates the role of surgical resection in select patients with SCLC, using a national cohort of approximately 2500 resected patients.

Methods: A retrospective study of SCLC patients in the National Cancer Data Base (NCDB) was performed where patients were grouped for comparison by stage and treatment regimen. Survival was estimated by Kaplan–Meier methods and multivariate comparisons using Cox regression.

Results: Of 28,621 cases of potentially resectable SCLC, 2476 patients (9%) underwent surgery of the primary site with curative intent. Five-year overall survival for patients after resection was 51%, 25%, and 18% for clinical stages I, II, and IIIA, respectively. Addition of surgery to chemotherapy was associated with decreased likelihood of death (hazard ratio: 0.57, 95% confidence interval: 0.47–0.68), independent of age, stage, and comorbidity score. Lobectomy was associated with a 5-year overall survival of 40% compared with 21% and 22% for sublobar resection and pneumonectomy, respectively. Hazard ratio for death after sublobar resections compared with lobectomy was 1.38 (95% confidence interval: 1.12–1.71).

Conclusions: Patients with stages I, II, and III SCLC, who underwent surgical resection as part of initial treatment with chemotherapy had respectable OS. These data may warrant prospective studies of including surgery in the multimodality treatment of SCLC in specific circumstances.

Key Words: Small-cell lung cancer, Surgery, Chemotherapy, Radiation therapy, Lobectomy, Sublobar resection.

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Small-cell lung cancer (SCLC) represents approximately 15% of all lung cancers, and 30,000 new diagnoses are made annually in the US.[1] SCLC often presents with rapid growth and early metastasis and consequently is also associated with a poor overall prognosis.[2] Select patients that present without distant metastasis and have disease confined to the ipsilateral chest are considered occasionally for curative intent resections, but their frequency are relatively rare. SCLC is highly sensitive to chemotherapy and radiation therapy, but local recurrences are reported as high as 50% in limited stage disease.[3,4] Several studies have investigated the role of surgery combined with chemotherapy and radiation therapy to improve local recurrence rates, but to mixed results.[5–7] Currently, the American College of Chest Physicians recommends surgery only in select stage I patients;[8] however, over the past 15 years, the use of surgery to treat SCLC has extended beyond this stage and thus remains controversial and without clear guidelines.

To investigate curative intent resections in a large national registry cohort, we defined potentially resectable disease as those patients with disease confined to the ipsilateral hemithorax and without evidence of distant disease. The purpose of this study was to analyze the prevalence of surgery for the primary site in patients with potentially resectable SCLC, to identify characteristics of patients who may benefit from surgery compared with patients treated with traditional regimens of systemic chemotherapy, and to compare different surgical procedures.

METHODS

Patient data was culled from the National Cancer Data Base (NCDB), a joint program of the American College of Surgeons Commission on Cancer and the American Cancer Society. The database contains approximately 26 million patients from more than 1500 participating institutions, and captures approximately 70% of newly diagnosed cancers in the United States annually.[9] Standardized collection and definition of data items has been previously described.[10,11] The NCDB collects data on patient and hospital characteristics, cancer diagnosis, staging, treatments, and outcomes. The data used in this study are derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators.

The study population included patients 18 years of age or older with no other history of malignancy diagnosed between 1998 and 2011. Patients were restricted to histologic diagnosis of invasive small-cell bronchogenic carcinoma confirmed by microscopic examination of tissue specimen or cytologic specimen, and *International Classification of Diseases for*

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Oncology, Third Edition (ICD-0–3) codes 8041 to 8044. To keep the relatively large data set pure, these criteria do not include patients with mixed NSCLC–SCLC histologies, such as small cell–large cell, small cell–adenocarcinoma, and small cell–squamous cell carcinoma nor NSCLC with neuroendocrine features. Clinical and pathological stages are reported according to the 7th edition of AJCC's tumor, node, metastases (TNM) staging criteria. Patients initially staged using the fifth or sixth editions in the NCDB were restaged using all available data on tumor characteristics recorded according to the AJCC-sponsored Collaborative Stage Data Collection System.[12] SCLC cases not originally staged under the seventh edition that were missing information allowing for restaging to the seventh edition were excluded.

Because the primary aim of this study was to evaluate outcomes related to surgical treatment of the primary site performed with curative intent, patients with evidence of metastatic disease, bilateral or midline only tumors, malignant pleural or pericardial effusions, lack of identifiable primary tumor (T0 or T occult), or clinical T4 and clinical N3 disease were excluded. To compare treatment groups, patients with unknown or undefined treatment history were excluded, including unknown chemotherapy or radiation therapy status, and surgical procedures such as "excision, NOS" and "resection, NOS."

Patients were compared in two treatment groups: primary surgical treatment and nonsurgical treatment. Patients treated with chemotherapy with or without radiation therapy, but without surgery, comprised the nonsurgical treatment group. Chemotherapy was defined by single- or multi-agent systemic chemotherapy as part of the first course of treatment. Radiation therapy was defined by beam radiation as part of the first course of treatment to a minimum dose of 45Gy, and patients with anatomic target volumes outside the thorax were not included in the radiation subgroup. The NCDB does not systematically record use of prophylactic cranial irradiation, so this information was not incorporated in this analysis. Patients who received chemotherapy or radiation therapy for palliation were not included in these groups.

The primary surgical treatment group included all patients who underwent resection of the primary site, and procedures were defined as sublobar resection, lobectomy, and pneumonectomy. Sublobar resections included wedge resections and segmental resections. Bronchial sleeve resections and bilobectomies were grouped under the lobectomy category. Surgery performed more than 180 days after diagnosis, patients who underwent surgical resection for palliation, and noncurative procedures, such as local tumor destruction and laser excision, were excluded from the surgery group. Treatment regimens for patients in the primary surgical treatment group were determined using NCDB codes for chemotherapy–surgery and radiation–surgery sequences. For patients without sequence codes, the number of days from diagnosis to definitive or first surgery and start of chemotherapy or radiation were used to calculate treatment sequences. Patients included in an unknown sequence group represent those who received both surgery and chemotherapy, but did not have dates of treatment or sequence codes.

The primary outcome of interest was the effect of surgical resection of the primary site on overall survival (OS). Disease-specific survival is not captured in the NCDB and, therefore, was not assessed. OS was estimated by the nonparametric Kaplan–Meier method and statistical differences between strata were evaluated using the log-rank test. Only clinical staging was used to compare surgical and nonsurgical patients. A multivariable Cox proportional hazards model with backward elimination of covariates with a p value greater than 0.05 was used to control for patient and tumor characteristics (age, sex, facility type, Charlson–Deyo score, location of tumor, laterality, clinical or pathologic T stage, N stage, and TNM stage) when evaluating the association of treatment with OS. Cox models were repeated with and without variables missing greater than 10% of patient data. To allow 5 years of follow-up for all patients before last data collection in 2011, all survival analysis was limited to patients diagnosed from 1998 to 2006. Patients alive at the end of the study were censored observations.

All statistical tests and analyses were performed using SAS v9.1 (SAS Institute, Cary, NC). p value less than 0.05 was used as the threshold for statistical significance.

RESULTS

Of 203,229 staged patients with histologic confirmation of SCLC, 35,927 (18%) met initial criteria for potentially resectable disease. Of these patients, 28,621 had documented surgical or systemic treatment and were included in further analysis. Median age was 66 years (range, 23–90). Patient data by treatment group are shown in Table 1.

Of the 2476 patients in the primary surgical treatment group, lobectomy was the most common procedure comprising 71% ($n = 1749$) of the surgical cohort. Twenty-four percent of patients (597) underwent a sublobar resection, the majority of which were wedge resections (535), whereas only 5% patients (130) had a pneumonectomy. Eighty-seven percent of patients (2158) had negative microscopic surgical margins by surgical pathology. Regional node surgery predominated with 92% of patients (2291) with recorded nodal surgery status at primary resection. The majority of surgical patients received chemotherapy, 68% (1679), and 20% (501) received radiation therapy in addition to surgery. Treatment regimens for the primary surgical and nonsurgical treatment groups are shown in Table 2. Of 1402 surgical patients with a recorded clinical stage, 77% of patients (1085) had the same pathologic stage, 4% of patients (50) had a lower pathologic stage, whereas 19% of patients (267) were upstaged. Fewer than 10 resected patients with clinical stages IA–IIIA were upstaged to pathologic stage IIIB, the remainder of pIIIB patients did not have a recorded clinical stage. Analysis of the patients diagnosed in 2007–2011, who lack verified 5-year follow-up and are not included in the following survival analysis, revealed an increase in the use of surgery in potentially resectable lesions to 10% (1008) from 8% for patients (1468) diagnosed before 2007 ($p < 0.0001$). In these resected patients, there was an increase in the frequency of sublobar resections compared with lobectomy, from 22% (323) to 27% (274), ($p = 0.0192$), whereas the incidence of pneumonectomy decreased from 7%

