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%

TABLE 1. Patient and Tumor Characteristics for SCLC Patients by Treatment Group

Variable	Level	Primary Surgical Treatment % (*n*)	Nonsurgical Treatment % (*n*)	Total, *n*
Age	<60	26 (638)	27 (6948)	7586
	60–75	59 (1457)	56 (14,665)	16,122
	Over 75	15 (381)	17 (4532)	4913
Sex	Men	45 (1111)	46 (11,980)	13,091
	Women	55 (1365)	54 (14,165)	15,530
Charlson–Deyo	0	34 (848)	39 (10,306)	11,154
Score[a]	1	27 (666)	17 (4462)	5128
	2+	10 (256)	7 (1822)	2078
	Not recorded	29 (706)	37 (9555)	10,261
Clinical TNM stage	IA	34 (841)	9 (2224)	3065
	IB	7 (168)	6 (1660)	1828
	IIA	8 (192)	11 (2863)	3055
	IIB	2 (43)	6 (1689)	1732
	IIIA	6 (158)	64 (16,848)	17,006
	Not recorded	43 (1074)	3 (861)	1935
Clinical T stage	cT1	50 (1232)	29 (7640)	8872
	cT2	22 (538)	44 (11,536)	12,074
	cT3	4 (88)	25 (6572)	6660
	Not recorded	25 (618)	2 (397)	1015
Clinical N Stage	cN0	37 (909)	22 (5816)	6725
	cN1	8 (197)	13 (3441)	3638
	cN2	6 (144)	61 (15,965)	16,109
	Not recorded	50 (1226)	4 (923)	2149
Laterality	Origin of primary is right	54 (1332)	59 (15,367)	16,699
	Origin of primary is left	46 (1144)	41 (10,778)	11,922
Primary site	Upper lobe	58 (1439)	57 (14,950)	16,389
	Middle lobe	6 (146)	6 (1488)	1634
	Lower lobe	33 (814)	26 (6724)	7538
	Overlapping lesion	1 (26)	2 (536)	562
	Not specified[b]	2 (51)	9 (2447)	2498
Facility type	Community Cancer Program (CCP)	11 (276)	15 (3817)	4093
	Comprehensive CCP	57 (1410)	61 (16,042)	17,452
	Academic/research program	31 (763)	22 (5774)	6537
	Other specified cancer programs	1 (27)	2 (512)	539
Year of diagnosis	1998–2002	29 (706)	37 (9555)	10,261
	2003–2006	31 (762)	28 (7259)	8021
	2007–2011	41 (1008)	36 (9331)	10,339
Pathologic TNM stage	IA	38 (953)		
	IB	13 (334)		
	IIA	22 (553)		
	IIB	5 (119)		
	IIIA	20 (483)		
	IIIB	1 (34)		
Pathologic T stage	pT1	58 (1424)		
	pT2	32 (787)		
	pT3	8 (188)		
	pT4	3 (77)		
Pathologic N stage	pN0	58 (1430)		
	pN1	25 (617)		
	pN2	17 (417)		
	Not recorded	<1 (12)		

[a]Only recorded for patients diagnosed from 2003 to 2011.
[b]Lung, not otherwise specified.
SCLC, small-cell lung cancer; TNM, tumor, node, metastases.

TABLE 2. Frequency of Treatment Regimens among Patient Groups

Treatment Regimens	Total % (*n*)
Primary surgical treatment (*n* = 2476)	
Neoadjuvant chemoradiation (CR-S)	<1 (12)
Neoadjuvant chemotherapy (C-S)	2 (40)
Adjuvant chemotherapy (S-C)	45 (1106)
Surgery without chemotherapy (S)	32 (796)
Adjuvant chemoradiation (S-CR)	17 (409)
Surgery with chemotherapy, unknown sequence	5 (113)
Nonsurgical treatment (*n* = 26,145)	
Chemotherapy only	45 (11,661)
Chemoradiation	55 (14,484)

CR, chemoradiation therapy; C, chemotherapy; S, surgery.

(103) to 3% (27) after 2006 ($p < 0.0001$). Diagnosis of SCLC and definitive surgery were recorded as the same day for 41% of patients (826), indicating these patients likely underwent surgery without pathologic diagnosis of SCLC.

Including only the patients diagnosed before 2007, 88% of patients (16,175 of 18,282) died, with a median survival of 15.9 months. Unadjusted Kaplan–Meier analysis showed significant differences in 5-year OS by treatment group in all clinical stages, with surgery plus chemotherapy having the best OS (Fig. 1). For these patients, 5-year OS was 51%, 25%, and 18% for clinical stages I, II and III, respectively. In analysis of stage A and B subgroups, clinical stage IA patients had the best survival, with 5-year OS of 54% after resection plus nonsurgical therapy compared with 18% after nonsurgical therapy ($p < 0.0001$). For clinical stage IB patients, surgery with chemotherapy had a 5-year OS of 36%, whereas survival after nonsurgical therapy was 19% ($p = 0.009$), similar to stage IA patients treated in the same fashion. For clinical stage IIA patients treated with surgery and chemotherapy, 5-year OS was 24%, whereas chemotherapy alone was associated with 5-year OS of 17%. Survival differences between treatment groups were not significant when 33 clinical stage IIB patients were analyzed separately ($p = 0.139$), with fewer than 10 patients undergoing both surgery and chemotherapy. In clinical stage IIIA patients, 5-year OS was 12% for nonsurgical therapy alone and 18% with the addition of surgery ($p = 0.047$, Fig. 1*C*). Analysis by Charlson–Deyo comorbidity score showed that patients treated with surgery and nonsurgical therapy had significantly improved survival, with 5-year OS of 43%, 40%, and 25% for comorbidity scores of 0, 1, and 2+ ($p < 0.0001$, Fig. 2). Among primary surgical patients, lobectomy was associated with an OS of 40%, compared with 21% and 22% for sublobar resections and pneumonectomy, respectively ($p < 0.0001$, Fig. 3). When comparing only pathologic stage I patients, 5-year OS was 49% after lobectomy versus 30% after a sublobar resection. Kaplan–Meier curves for patients who underwent lobectomy are shown by pathologic stage in Figure 4. For comparison, 5-year OS was 5% for both patients with metastatic or otherwise nonresectable disease at diagnosis ($n = 122,484$), as well as patients with potentially resectable disease, who received neither surgery nor chemotherapy ($n = 3408$). Although these groups may illustrate the natural history of SCLC, they represent an alternative treatment paradigm and were not included in our analysis.

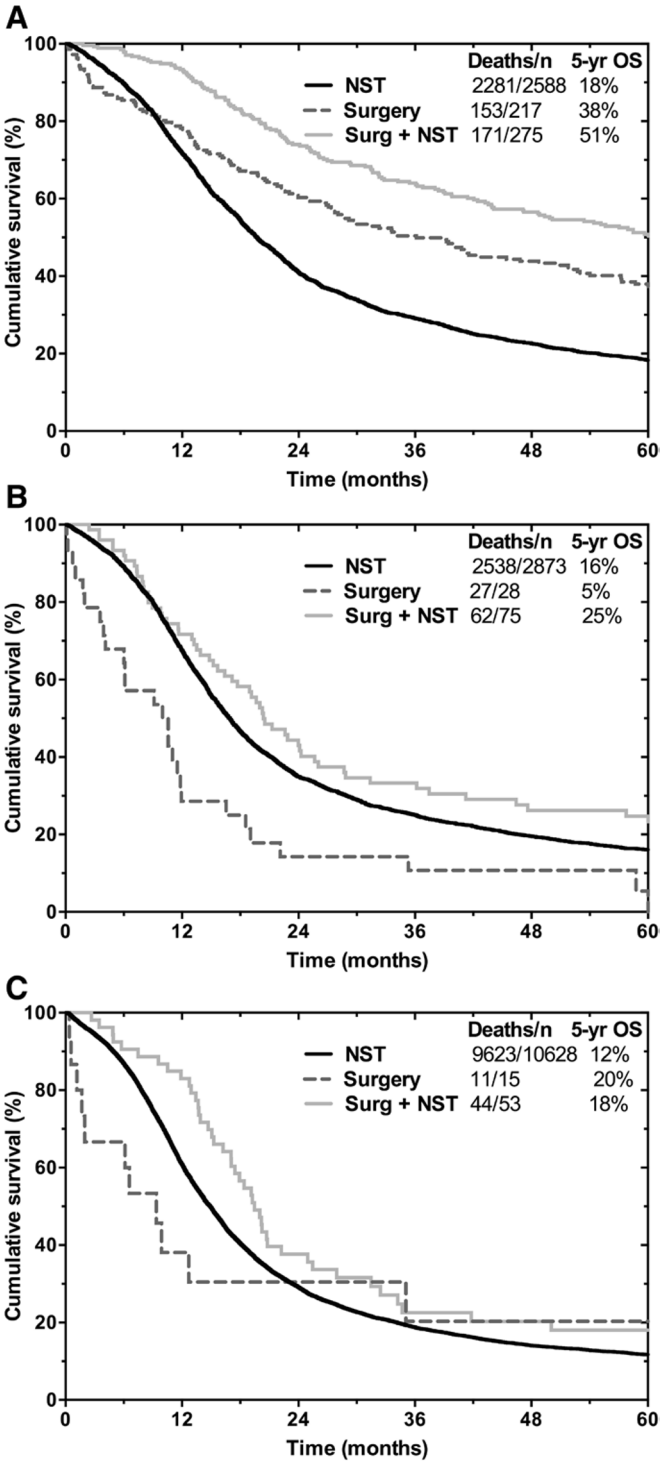

FIGURE 1. Kaplan–Meier curve for overall survival by clinical stage I (*A*), II (*B*), and IIIA (*C*) patients by treatment, including NST, surgery alone, or surgery with NST (Surg + NST). NST, nonsurgical therapy.

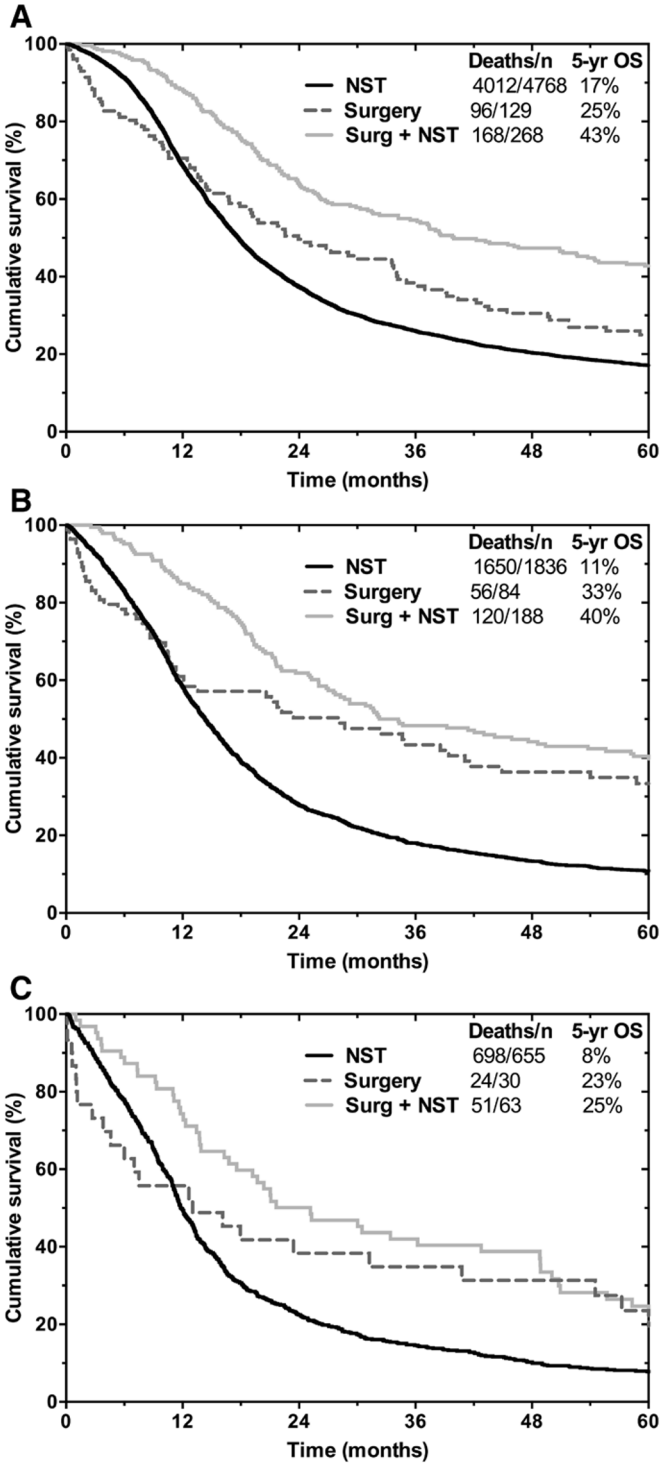

FIGURE 2. Kaplan–Meier curve for overall survival by Charlson–Deyo score of 0 (*A*), 1 (*B*), and 2+ (*C*) by treatment, including NST, surgery alone, or surgery with NST (Surg + NST). NST, nonsurgical therapy.

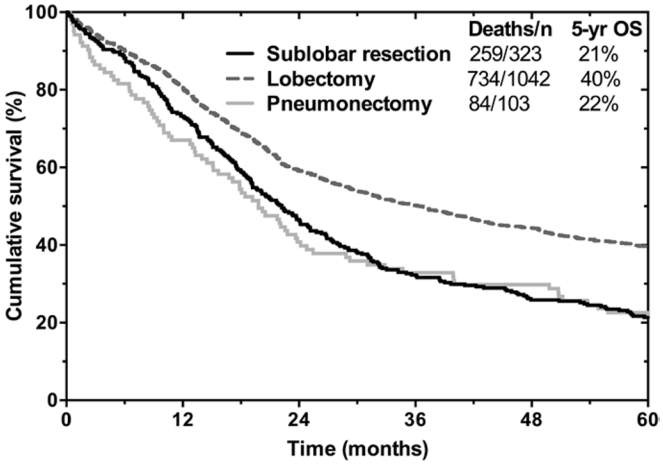

FIGURE 3. Kaplan–Meier curve for overall survival of primary surgical treatment patients by type of surgical procedure.

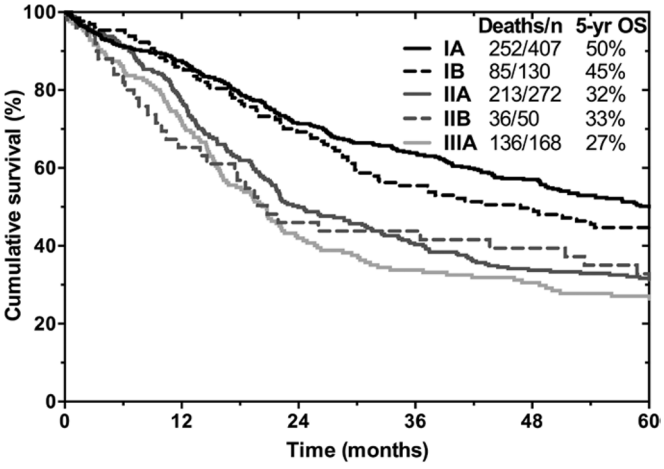

FIGURE 4. Kaplan–Meier curve for overall survival of lobectomy patients by pathologic stage.

When controlling for patient and tumor characteristics, independent predictors of survival included age, sex, stage, and Charlson–Deyo Score (Table 3). For patients who received chemotherapy, hazard ratio (HR) was lower for those who also underwent surgery compared with those who were treated with nonsurgical therapy alone (HR: 0.57, 95% confidence interval: 0.47–0.68). In the primary surgical treatment group, improved outcomes were associated with adjuvant chemotherapy sequences when compared with surgery alone (Table 3). When procedure types were compared, sublobar resection was significantly associated with increased likelihood of death compared with lobectomy (HR: 1.38, 95% confidence interval: 1.12–1.71). Charlson–Deyo score was not collected for patients diagnosed before 2003 (56%). Both models were rerun without Charlson–Deyo score to include patients diagnosed before 2003, and there were no changes in the predicting factors or trends (data not shown). The models shown incorporate the comorbidity score for completeness.

DISCUSSION

SCLC is a rapidly progressive malignancy with a median survival of 17 months and 5-year OS of 10% for approximately

TABLE 3. Cox Proportional Hazards for Mortality for Overall Cohort and Primary Surgical Treatment Group

Characteristic	Hazard Ratio	95% CI	*p* Value
Overall cohort			
Age (ref = <60)			
60–75	1.28	1.20–1.36	<0.0001
Over 75	1.87	1.72–2.03	<0.0001
Sex (ref = men)			
Female	0.85	0.81–0.90	<0.0001
Charlson–Deyo score (ref = 0)			
1	1.31	1.23–1.39	<0.0001
2+	1.56	1.43–1.71	<0.0001
Clinical T Stage (ref = cT1)			
cT2	1.19	1.11–1.27	<0.0001
cT3	1.30	1.21–1.39	<0.0001
Clinical N Stage (ref = cN0)			
N1	1.12	1.02–1.23	0.0138
N2	1.38	1.29–1.47	<0.0001
Treatment (ref = chemotherapy only)			
Surgery + chemotherapy	0.57	0.47–0.68	<0.0001
Surgery only	0.95	0.75–1.21	0.6731
Primary surgical treatment group			
Age (ref = <60)			
60–75	1.61	1.27–2.05	<0.0001
Over 75	2.47	1.85–3.3	<0.0001
Charlson–Deyo score (ref = 0)			
1	1.04	0.85–1.28	0.692
2+	1.76	1.34–2.3	<0.0001
Primary tumor site (ref = upper lobe)			
Lower lobe	1.36	1.13–1.65	0.002
Middle lobe	1.51	0.99–2.32	0.057
Overlapping lesion	4.31	1.96–9.52	0.0003
Pathologic T Stage (ref = pT1)			
T2	1.19	0.96–1.46	0.106
T3	1.84	1.32–2.58	0.0004
T4	1.1	0.62–1.95	0.749
Pathologic N Stage (ref = pN0)			
N1	2.21	1.75–2.79	<0.0001
N2	2.7	2.05–3.56	<0.0001
Treatment sequence (ref = surgery only)			
Neoadjuvant chemoradiation (CR-S)	0.51	0.07–3.71	0.505
Neoadjuvant chemotherapy (C-S)	0.61	0.31–1.21	0.160
Adjuvant chemoradiation (S-CR)	0.41	0.31–0.56	<0.0001
Adjuvant chemotherapy (S-C)	0.53	0.43–0.65	<0.0001
Surgical procedure (ref = lobectomy)			
Sublobar resection	1.38	1.12–1.71	0.003
Pneumonectomy	1.22	0.84–1.78	0.297

CI, confidence interval.

40% of patients who present with nonmetastatic disease.[13,14] Current therapies for most patients include platinum-based chemotherapy, with or without radiation, but the role of surgery in treatment of SCLC remains controversial, as the disease is typically treated as systemic, even without clinical evidence of metastatic disease. This analysis represents a highly select group of patients with early diagnosis of SCLC, and the inherent selection bias of patients who are candidates

for surgery must be acknowledged when comparing patients who underwent resection versus nonsurgical therapy alone. Only 18% of patients in this NCDB cohort met criteria for potentially resectable disease, and fewer than 10% of these patients underwent primary resection with curative intent, including sublobar resection, lobectomy, and pneumonectomy.

In this population, the improved survival of potentially resectable SCLC patients treated with surgery and chemotherapy mirrors that of NSCLC patients. NSCLC 5-year OS for pathologic stages I, II, and III is 66%, 41%, and 23%, respectively.[15] In comparison, SCLC patients treated with multimodality therapy including surgery had survival rates of 49%, 32%, and 27% for the same pathologic stages, respectively. Similar results were noted in the UK population analyzed by Lüchtenborg et al.[16] who found a 31% 5-year OS in resected SCLC of all stages, compared with 45% in resected NSCLC patients. When compared with clinical stage, surgical patients in this study demonstrated improved survival compared with patients of the same clinical stage treated with standard nonsurgical therapy. The rationale for using clinical stage for survival analysis was that it allowed for comparisons to the majority of patients who are treated without pathologic staging, i.e., underwent nonsurgical therapy. However, recommendations from the American College of Chest Physicians (ACCP) indicate surgical resection only for patients with clinical stage I SCLC (T1-2, N0), followed by chemotherapy.[8] The National Comprehensive Cancer Network (NCCN) guidelines similarly recommend surgery with adjuvant chemotherapy only for stage I disease, and specify that lobectomy is the preferred resection procedure.[17] Stage I surgical patients in the SEER database were associated with a range of 5-year OS from 34% to 57% depending on type of resection and use of radiotherapy, and other stage I studies found an average 5-year OS of 52%.[18] Small groups of only confirmed pathologic stage I patients after surgery have demonstrated survival ranging from 48% to 86%.[19,20] Overall, the use of surgery in this population remains low despite evidence and guidelines recommending surgery. In this cohort, only 21% of stage I patients had surgical resection.

In addition to stage I patients, this investigation indicates that certain patients with clinical stage II and III disease may also benefit from surgical resection as part of their treatment strategy. These data are consistent with an earlier report by Schreiber et al.[21] showing a 26% 5-year OS for T3/T4 or N1/N2 SCLC after surgery, compared with 9% among similarly staged patients without resection. Additional smaller series have demonstrated clear survival benefit for adding surgery in N1 and N2 patients.[22,23] Using an earlier NCDB cohort from 1992 to 2002, Gaspar et al.[24] demonstrated a benefit for surgery combined with nonsurgical treatment, compared with chemoradiation therapy alone in stage I and II patients (HR: 2.0), and also in stage III patients (HR: 1.49). This evidence suggests that stage II and III patients could be included in further studies to identify specific candidates in whom surgical therapy may be advantageous.

Few prospective trials have investigated surgical resection in SCLC. The only published randomized controlled trial by the Lung Cancer Study Group in the 1980s did not demonstrate a benefit in surgical treatment for SCLC.[6] In this study, 146 limited stage patients with partial response to induction chemotherapy were randomized to surgery or no surgery, with median survival of 15.4 and 18.6 months, respectively. Application of this study to negate a role for surgery has been criticized based on the intent to treat model, which included over 30% of patients in the surgical arm who did not undergo a complete resection. In addition, the study took place before widespread use of platinum-based chemotherapy and staging mediastinoscopy.[21,23] A phase II trial by Eberhardt et al. treated 46 patients, stages IA–IIIB, with multimodal therapy. After induction chemotherapy with or without radiation therapy, patients with complete nodal response by a restaging mediastinoscopy were eligible for resection. The resection group of 23 patients, stage IB–IIIA, had a 5-year OS of 63%, with 100% local control in completely resected patients, although 9 patients (36%) had distant recurrence.[7]

Our data indicate that sublobar resections result in worse outcomes than lobectomy, with 5-year OS of 30% and 49%, respectively, in stage I patients. Across all stages lobectomy patients had a 40% 5-year OS, compared with 21% for sublobar resection. In this study, approximately 24% of all resected patients (26% of resected stage I patients) underwent sublobar resections. Similarly, patients from the SEER database had median survival of 23 months for sublobar resection versus 40 months for lobectomy in all limited stage cases, and in the subset of stage I patients, lobectomy was superior to sublobar resection, with a 5-year OS of 50% and 34%, respectively.[18,21] Overall, these findings suggest that sublobar resection for SCLC may be suboptimal in the treatment of SCLC patients whether or not they have a preoperative diagnosis of SCLC.

The majority of resected patients also received chemotherapy, although 32% underwent resection without additional systemic therapy. The most common regimens were adjuvant chemotherapy and adjuvant chemoradiation therapy, which were both associated with significant benefit in multivariate analysis of the surgical group. The surgical studies discussed above have included multiple combinations of chemotherapy and radiation therapy used in both neoadjuvant and adjuvant settings. For some surgical patients, pathologic stage may represent downstaging after neoadjuvant therapy. It is unclear why about a third of patients did not undergo adjuvant therapy, despite NCCN and AJCC guidelines recommending chemotherapy in all stages. Further investigation is required to determine which treatment paradigms optimize survival in each stage of SCLC.

Although our investigation was retrospective, it is the largest analysis of SCLC patients treated with surgery thus far, and accounts for important modifiers that many other studies were unable to assess. Limitations of our study include the incomplete nature of a large national database and our inability to confirm reported data such as staging and treatment. Although we selected only cases with pure SCLC histologic codes and microscopic confirmation to exclude other pathologies such as carcinoid and mixed NSCLC–SCLC tumors, we cannot exclude the possibility that some cases were incorrectly diagnosed or recorded. Also, the rationale for why

some patients underwent sublobar resections as their surgical therapy was not explored due to the absence of granular information signifying cardiac or pulmonary status such as echocardiographic results or pulmonary function testing, respectively.

Although this study demonstrates that surgery is associated with improved OS in select patients when used as a part of multimodality treatment paradigm with chemotherapy with or without radiation therapy, local or distant recurrence or disease-specific mortality could not be assessed. Thus, the uncensored cohort includes patients alive with disease. In addition, survival analyses include only patients diagnosed before 2007. Finally, the impact of surgical complications and their effect on OS or functional recovery was not evaluated. We caution readers to interpret the results of this study within the context of these limitations, and we expect that future investigations will address remaining questions.

Overall, the primary surgical cohort represents a small subgroup of SCLC patients who present with a potentially resectable primary tumor and no evidence of metastatic disease. Although the NCDB does not have sufficient data to investigate this, the authors speculate that patients selected for resection represented a lower risk population who were likely to have a better outcome with any mode of therapy, and we acknowledge that this enhances the survival differences between patients treated with and without surgery. Patients selected for resection likely had less tumor burden, higher performance status, and less comorbidity. Still, the survival benefit for surgical treatment was evident for patients with Charlson–Deyo scores of 1 and 2 or higher, and in multivariate analysis surgery remained independently predictive of reduced mortality. A prospective trial may more clearly identify patient and tumor characteristics associated with improved outcome after primary resection.

In conclusion, this study supports a role for surgery in highly selected patients, including some with stage II and III, node positive SCLC. In addition, the data strongly support the use of lobar resection for all surgery with curative intent, and the eschewing of wedge and other sublobar resections for these patients. These data, with over 28,000 patients and nearly 2500 surgical cases, may justify additional prospective studies to further clarify the role of surgery in SCLC and to identify the patients who will benefit from the inclusion of primary resections in multimodality therapies.

REFERENCES

1. American Cancer Society. Cancer Facts and Figures. 2010. Atlanta: American Cancer Society, 2010.
2. van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. *Lancet* 2011;378:1741–1755.
3. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;327:1618–1624.
4. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:265–271.
5. Fox W, Scadding JG. Treatment of oat-celled carcinoma of the bronchus. *Lancet* 1973;2:616–617.
6. Lad T, Piantadosi S, Thomas P, et al. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. *Chest* 1994; 106:320S–323S.
7. Eberhardt W, Stamatis G, Stuschke M, et al. Prognostically orientated multimodality treatment including surgery for selected patients of small-cell lung cancer patients stages IB to IIIB: Long-term results of a phase II trial. *Br J Cancer* 1999;81:1206–1212.
8. Jett JR, Schild SE, Kesler KA, et al. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143:e400S–e419S.
9. National Cancer Data Base. http://www.facs.org/cancer/ncdb/index.html. Accessed January 14, 2014.
10. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: A powerful initiative to improve cancer care in the United States. *Ann Surg Oncol* 2008;15:683–690.
11. Commission on Cancer. Facility Oncology Registry Data Standards (FORDS): Revised for 2012. Chicago: American College of Surgeons Commission on Cancer; 2002.
12. Collaborative Stage Work Group of the American Joint Committee on Cancer. Collaborative Stage Data Collection System User Documentation and Coding Instructions, Version 02.04.40. Published by American Joint Committee on Cancer. Chicago, IL.
13. Jänne PA, Freidlin B, Saxman S, et al. Twenty-five years of clinical research for patients with limited-stage small cell lung carcinoma in North America. *Cancer* 2002;95:1528–1538.
14. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol* 2006;24:4539–4544.
15. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007; 2:706–714.
16. Lüchtenborg M, Riaz SP, Lim E, et al. Survival of patients with small cell lung cancer undergoing lung resection in England, 1998–2009. *Thorax* 2014;69:269–273.
17. Kalemkerian GP, Akerley W, Bogner P, et al. Small cell lung cancer. *J Natl Compr Canc Netw* 2013; 11:78–98.
18. Yu JB, Decker RH, Detterbeck FC, et al. Surveillance epidemiology and end results evaluation of the role of surgery for stage I small cell lung cancer. *J Thorac Oncol* 2010; 5:215–219.
19. Brock MV, Hooker CM, Syphard JE, et al. Surgical resection of limited disease small cell lung cancer in the new era of platinum chemotherapy: Its time has come. *J Thorac Cardiovasc Surg* 2005;129:64–72.
20. Vallières E, Shepherd FA, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009; 4:1049–1059.
21. Schreiber D, Rineer J, Weedon J, et al. Survival outcomes with the use of surgery in limited-stage small cell lung cancer: Should its role be re-evaluated? *Cancer* 2010;116:1350–1357.
22. Badzio A, Kurowski K, Karnicka-Mlodkowska H, Jassem J. A retrospective comparative study of surgery followed by chemotherapy vs. non-surgical management in limited-disease small cell lung cancer. *Eur J Cardiothorac Surg* 2004;26:183–188.
23. Lim E, Belcher E, Yap YK, et al. The role of surgery in the treatment of limited disease small cell lung cancer: Time to reevaluate. *J Thorac Oncol* 2008; 3:1267–1271.
24. Gaspar LE, McNamara EJ, Gay EG, et al. Small-cell lung cancer: Prognostic factors and changing treatment over 15 years. *Clin Lung Cancer* 2012;13:115–122.

