Surgery Versus Optimal Medical Management for N1 Small Cell Lung Cancer

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Background. **Adjuvant chemotherapy has been demonstrated to improve the outcomes of patients with N1 non-small cell lung cancer. It is unknown whether patients previously thought to have unresectable small cell lung cancer (SCLC) may have tumors amenable to surgery if adjuvant therapies can be given. This study was undertaken to evaluate whether surgery, in the setting of modern adjuvant therapies, can be beneficial for patients with N1-positive SCLC.**

Methods. **Patients with clinical T1–3 N1 M0 SCLC who underwent concurrent chemoradiation versus surgery and adjuvant therapy in the National Cancer Data Base from 2003 to 2011 were examined. Overall survival was assessed using Kaplan-Meier and Cox proportional hazards analysis and propensity score-matched analysis.**

Results. **Of 1,041 patients with cT1–3 N1 M0 SCLC who met inclusion criteria, 96 patients (9%) underwent surgery and adjuvant chemotherapy with or without radiation and 945 (91%) underwent concurrent chemoradiation alone. Multivariable Cox modeling demonstrated that surgery with adjuvant chemotherapy with or without radiation (hazard ratio 0.74, 95% confidence interval: 0.56 to 0.97) was associated with improved survival compared with concurrent chemoradiation. After propensity matching, surgery with adjuvant chemotherapy with or without radiation was associated with improved 5-year survival compared with concurrent chemoradiation (31.4% versus 26.3%).**

Conclusions. **In an analysis of a national population-based cancer database, surgery followed by adjuvant chemotherapy with or without radiation for cT1–3 N1 SCLC had improved outcomes compared with concurrent chemoradiation. These results support the re-evaluation of the role of surgery in multimodality therapy for N1 SCLC in a clinical trial setting.**

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Historically, surgery has not been indicated for the treatment of small cell lung cancer (SCLC). This is in large part due to the findings of two influential randomized controlled trials performed in the 1960s and 1980s that reported no improvement in survival for patients randomized to undergo surgery when compared to patients who underwent nonoperative management [1, 2]. However, recently, in small subsets of patients with limited-stage SCLC who undergo surgery, retrospective studies have reported more favorable 5-year survival rates [3–7], with 5-year survival as high as 86% for patients with stage I SCLC who received platinum-based adjuvant chemotherapy [5]. As a result, the National Comprehensive Cancer Network (NCCN) guidelines now recommend surgery as the initial treatment for patients with node-negative early stage SCLC [8].

It remains unclear, however, whether there is a role for surgery in patients with N1 disease. Current NCCN guidelines recommend concurrent chemoradiation for patients with N1 limited-stage SCLC [8], but these guidelines are based on limited data. In fact, in the era of modern platinum-doublet chemotherapy and radiation, there have been no published studies, randomized or retrospective, evaluating surgery versus concurrent chemoradiation for the subset of limited-stage patients with N1 SCLC.

The objective of this study was to assess outcomes of patients who underwent concurrent chemoradiation or surgery with adjuvant chemotherapy for T1–3 N1 M0 SCLC using the National Cancer Data Base (NCDB). Our hypothesis was that surgery, in the setting of modern adjuvant therapies, may be associated with superior

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survival when compared with a nonoperative approach for selected patients with limited-staged N1 SCLC.

Patients and Methods

National Cancer Data Base

The NCDB, which is a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society, includes approximately 70% of all newly diagnosed cases of cancer nationwide and contains data collected from more than 1,500 cancer program registries in the United States and Puerto Rico [9]. Clinical staging information is directly recorded in the NCDB using American Joint Committee on Cancer sixth and seventh editions TNM classifications for the years of study inclusion (2003 to 2011) [10].

Study Design

This NCDB study was approved by the Duke University Institutional Review Board. Inclusion criteria included all patients in the NCDB diagnosed with clinical T1–3 N1 M0 from 2003 to 2011 who underwent either concurrent chemoradiation or surgery and adjuvant therapy. Patients were identified using International Classification of Diseases for Oncology, third edition, histologic and topographic codes. This study period was chosen for the following two reasons: (1) the NCDB reports data on the Charlson/Deyo comorbidity condition (CDCC) score only for cases diagnosed from 2003 and after, and (2) survival data were available for cases diagnosed up to 2011.

Methods of follow-up were described previously [11]. To minimize confounding, the cohort was limited to patients who were initially diagnosed with a single malignancy of SCLC. Patients who were not diagnosed or treated at the reporting facility were excluded because the Commission on Cancer does not require follow-up for these cases. Additional exclusion criteria comprised patients who received chemotherapy or radiation before surgery, patients for whom the extent of resection was not recorded, and patients who were coded as having received palliative-intent treatment. The primary outcome was overall survival (OS).

Statistical Analysis

Patients with clinical T1–3 N1 M0 SCLC were grouped according to treatment (surgery with adjuvant chemotherapy with or without radiation or concurrent chemoradiation). Differences in median survival and 5-year survival were evaluated by the Kaplan-Meier product limit approach and the log-rank test.

A Cox proportional hazards regression model was used to further evaluate OS among the patient population. All covariates that were chosen for inclusion in the model were determined a priori to be clinically significant. Covariates included in the model included the following: treatment (surgery with adjuvant chemotherapy with or without radiation or concurrent chemoradiation), age, sex, race (white, black, or other), year of diagnosis, patient census tract median household income (<$38,000, $38,000 to $47,999, $48,000 to $62,999, or ≥$63,000), urban versus nonurban area for patient residence, treatment facility type (community cancer program, comprehensive community cancer program, or academic/research program), hospital volume (divided into quartiles), CDCC score (0, 1, or ≥2), and clinical T status. Because there were no patients in the surgical group who were treated at an unknown facility type and fewer than 10 patients in the chemoradiation group who were treated at an unknown facility type, patients treated at an unknown facility type were not included in the Cox model. A Cox model using the same covariates described above was used to evaluate OS, stratified by adjuvant chemotherapy without radiation versus adjuvant chemoradiation, among the surgical group.

Propensity score-matched analysis was used to create a cohort of patients who underwent surgery with adjuvant chemotherapy with or without radiation with similar baseline characteristics to patients who received concurrent chemoradiation, to attempt to control for nonrandom differences between the two groups in the overall cohort, as previously described [12]. In brief, a logistic regression model was used to calculate propensity scores based on the same covariates used in the Cox model described above. A radius-matching algorithm with a caliper of 0.01 was then used to find the most appropriately matched pairs. After matching, balance between groups was evaluated with standardized differences. Kaplan-Meier analysis was used to compare OS between the groups.

Subgroup analyses were then performed. We first performed propensity-matched analysis on the subgroup of patients who had T1 N1 tumors and on the subgroup of patients who had T2 N1 tumors. We then evaluated the impact of the extent of resection on OS, using Kaplan-Meier analysis and a multivariable Cox model with the following covariates: treatment (wedge versus lobectomy), age, sex, race, clinical T status, CDCC score, year of diagnosis, patient census tract median household income, urban versus nonurban area for patient residence, treatment facility type, and hospital volume. All statistical analyses were performed using Stata/MP software, version 13.1 for Mac (StataCorp, College Station, TX). A two-sided p value of 0.05 was used to define significance.

Results

Between 2003 and 2011, 4,490 patients were diagnosed with clinical T1–3 N1 M0 SCLC. Among these, 1,041 patients (23.2%) met study inclusion criteria (Fig 1). Of these 1,041 patients, concurrent chemoradiation was administered to 945 patients (90.8%), whereas 96 patients (9.2%) underwent surgery with adjuvant chemotherapy with or without radiation. In the surgery group, 44 patients (47.8%) received adjuvant chemotherapy, whereas 52 patients (54.2%) received adjuvant chemoradiation; of these 52 patients, 25 patients (48.1%) received sequential chemoradiation (20 patients received radiation to the lung and 5 patients received radiation to the brain) and 27 patients (51.9%) received concurrent chemoradiation (26 patients received radiation to the lung and 1 patient received radiation to the brain). Because patients with

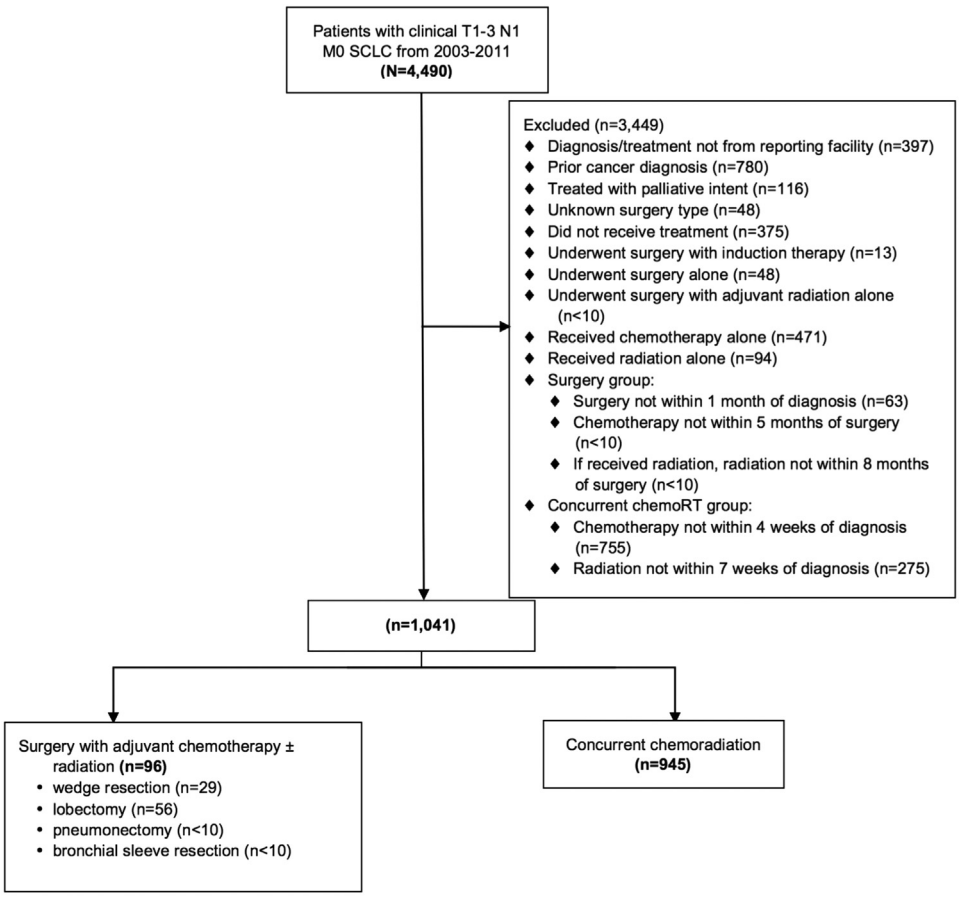

Fig 1. Consolidated Standards of Reporting Trials (CONSORT) diagram showing schema of study subject selection (clinical T1–3 N1 M0 patients). (RT = radiation; SCLC = small cell lung cancer.)

metastatic disease were excluded from the cohort, patients who received cranial irradiation presumably received prophylactic cranial irradiation. Among patients receiving adjuvant radiation to the lung, it is not known how many patients received additional prophylactic radiation to the brain.

Supplemental Table 1A shows the preoperative and demographic characteristics of the patient cohort. There was a higher proportion of patients in the surgery group at academic/research facilities than patients in the concurrent chemoradiation group. There were more surgical patients with a CDCC score of 1, whereas more concurrent chemoradiation patients had CDCC scores of 0 or $\geq$2. Surgical patients also had lower clinical T status than concurrent chemoradiation patients.

The pathologic results and short-term outcomes of the patient cohort are presented in Supplemental Table 1B. In the surgical group, 36 patients (37.5%) had pathologic T1 disease, 38 patients (39.6%) had pathologic T2 disease. Pathologic T status was unknown for 12 patients (12.5%) in the surgical group and for 863 patients (91.3%) in the concurrent chemoradiation group. Patients in the surgical group had more lymph nodes examined and lower tumor size than patients in the chemoradiation group. Eleven patients (11.5%) in the surgical group and fewer than 10 patients in the chemoradiation group were upstaged to pathologic N2 disease. Ten patients (10.4%) in the surgical group were downstaged to pathologic N0 disease. In patients who underwent wedge resection, 5 patients (17.2%) had positive margins (2 patients had microscopic positive margins and 3 patients had residual tumor not otherwise specified). In patients who underwent a lobectomy, 10 patients (17.9%) had positive microscopic margins (5 patients had microscopic positive margins and 5 patients had residual tumor not otherwise specified).

The median follow-up for the entire cohort was 22 months (interquartile range, 12 to 43 months). Compared with concurrent chemoradiation, treatment with surgery and adjuvant chemotherapy with or without radiation was associated with significantly better survival for clinical T1–3 N1 M0 SCLC patients (Fig 2). Kaplan-Meier analysis demonstrated a 5-year survival of 31.6% for the surgery group and 27.9% for the concurrent chemoradiation group (log-rank $p = 0.03$). After multivariable adjustment, treatment with surgery and adjuvant chemotherapy with or without radiation was significantly associated with improved survival (hazard ratio [HR] 0.74, 95% confidence interval [CI]: 0.56 to 0.98, $p = 0.04$) (Supplemental Table 3A).

Comparison of patient characteristics and outcomes after propensity matching between patients who underwent surgery with adjuvant chemotherapy with or without radiation and patients who received concurrent chemotherapy is shown in Supplemental Tables 2A and 2B. The propensity

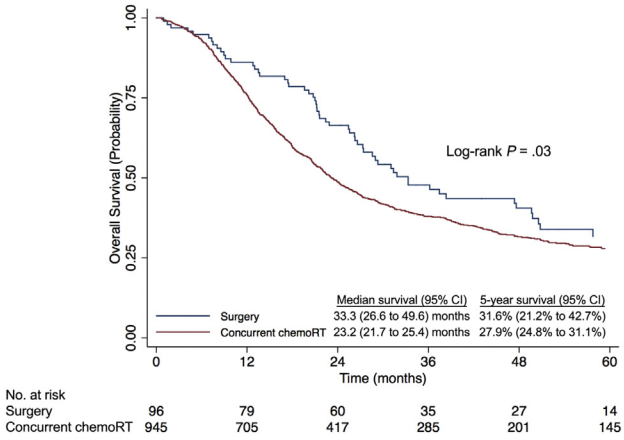

Fig 2. Overall survival of cT1–3 N1 M0 small cell lung cancer (SCLC) patients, stratified by surgery versus concurrent chemoradiation. (CI = confidence interval; RT = radiation.)

score matching created a population of 87 patients who underwent surgery with adjuvant chemotherapy with or without radiation and 87 patients who received concurrent chemoradiation. After matching, no significant differences were found between the preoperative and demographic characteristics for the two groups. All standardized mean differences decreased to less than 0.2.

After the match, patients who underwent surgery with adjuvant chemotherapy with or without radiation had significantly higher median OS (33.3 months [95% CI: 26.6 to 49.8 months] versus 21.1 months [95% CI: 15.2 to 29.3 months]) and 5-year OS (31.4% [95% CI: 20.5% to 42.8%] versus 26.3% [95% CI: 16.9% to 36.5%]) (log-rank $p = 0.03$) than patients who received concurrent chemoradiation (Fig 3). No significant difference in tumor size was found between the groups.

Among the surgery group, treatment with adjuvant chemoradiation was associated with significantly better survival than treatment with adjuvant chemotherapy

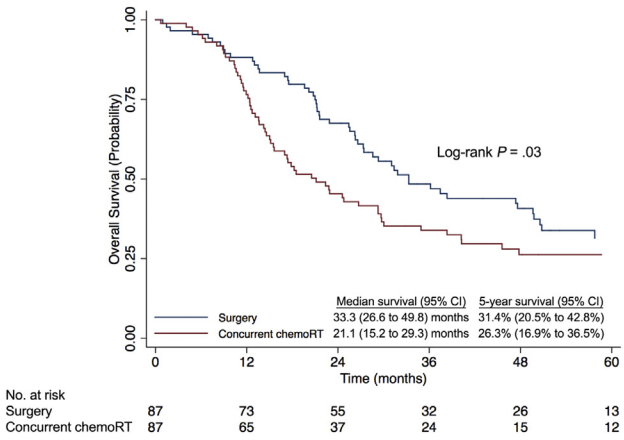

Fig 3. Overall survival of cT1–3 N1 M0 small cell lung cancer (SCLC) patients, stratified by surgery versus concurrent chemoradiation: propensity score-matched analysis. (CI = confidence interval; RT = radiation.)

without radiation after multivariable adjustment (HR 0.44, 95% CI: 0.23 to 0.85, $p = 0.01$) (Supplemental Table 3B).

Among patients who underwent surgery, most underwent a wedge resection (n = 29) or a lobectomy (n = 56), and fewer than 10 patients underwent a pneumonectomy or a sleeve lobectomy. No patients underwent a segmentectomy. In unadjusted analysis, there were no differences in survival between patients who underwent a wedge resection and patients who underwent a lobectomy (Figs 4A, 4B). However, in a multivariable analysis comparing wedge resection with lobectomy, lobectomy was associated with improved survival (HR 0.40, 95% CI: 0.20 to 0.82, $p = 0.01$).

In a subgroup analysis limited to patients with T1 N1 tumors, we propensity matched 43 patients in each arm. After matching, no significant differences were found between the preoperative and demographic characteristics for the two groups (data not shown). We found that compared with concurrent chemoradiation, surgery was associated with improved OS ($p = 0.02$). Median survival in the surgery group was 36.2 months [95% CI: 27.3 months to not applicable] versus 23.9 months [95% CI: 18.4 to 34.5 months] in the concurrent chemoradiation group. Five-year survival for the surgery group was 35.6% [95% CI: 20.0% to 51.6%] versus 20.2% [95% CI: 8.3% to 35.8%] for the concurrent chemoradiation group.

In a subgroup analysis limited to patients with T2 N1 tumors, we propensity matched 36 patients in each arm. After matching, no significant differences were found between the preoperative and demographic characteristics for the two groups (data not shown). We found that compared with concurrent chemoradiation, surgery was associated with a trend toward improved median survival (log-rank $p = 0.09$). Median survival was 33.3 months [95% CI: 21.2 to 49.8 months] in the surgery group and 17.8 months [95% CI: 12.0 to 31.2 months] in the concurrent chemoradiation group. Five-year survival was 28.7% [95% CI: 13.9% to 45.5%] in the surgery group compared with 20.6% [95% CI: 8.0% to 37.4%] in the concurrent chemoradiation group. In a subgroup analysis limited to patients with no comorbidities, we found that surgery (n = 51) was associated with a trend toward improved survival compared with concurrent chemoradiation (n = 625) (log-rank $p = 0.17$) (Fig 5). Median survival was 33.3 months [95% CI: 26.3 to 57.8 months] in the surgery group and 25.7 months [95% CI: 23.2 to 29.3 months] in the concurrent chemoradiation group. Five-year survival was 32.9% [95% CI: 18.5% to 48.1%] in the surgery group compared with 29.4% [95% CI: 25.5% to 33.4%] in the concurrent chemoradiation group.

Comment

This study evaluated the impact of surgery versus concurrent chemotherapy and radiation for N1 SCLC. Both multivariable Cox modeling and propensity score-matched analysis demonstrated that surgery was associated with a significantly higher OS than concurrent chemoradiation for patients with clinical T1–3 N1 M0 SCLC. After multivariable adjustment, treatment with

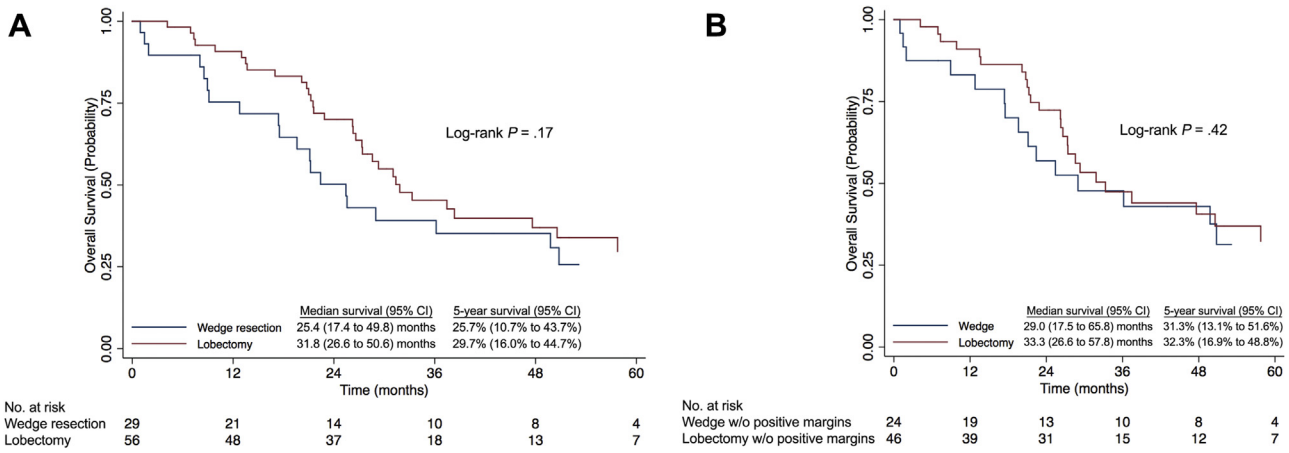

Fig 4. (A) Overall survival of cT1–3 N1 M0 small cell lung cancer (SCLC) patients who underwent wedge resection versus lobectomy. (B) Overall survival of cT1–3 N1 M0 SCLC patients who underwent wedge resection or lobectomy and did not have positive margins. (CI = confidence interval.)

adjuvant chemoradiation was found to be associated with significantly better survival than treatment with adjuvant chemotherapy without radiation.

Current NCCN guidelines recommend concurrent chemoradiation for patients with limited stage (including T1–3 N1 M0) SCLC. The data to support this recommendation are limited. There have been two randomized controlled trials performed more than two decades ago that evaluated surgery versus nonoperative management for SCLC [1, 2]. In 1973, results of the Medical Research Council randomized trial evaluating surgery versus radiotherapy for SCLC found that patients randomized to radiation treatment (n = 73) had better long-term survival than patients who were randomized to the surgical arm (n = 71), although the survival was poor in both groups (5-year survival: 4% versus 1%) [2]. In 1994, the Lung Cancer Study Group found that patients with limited stage SCLC with regional lymph node involvement who received neoadjuvant chemotherapy followed by surgery (n = 70) did not have better survival than patients who had neoadjuvant chemotherapy followed by definitive radiation (n = 76) [1]. The study found that the 2-year OS in both the surgery and radiation groups was 20%. From these studies, it appeared that there was no role for surgery in the multimodality treatment of SCLC.

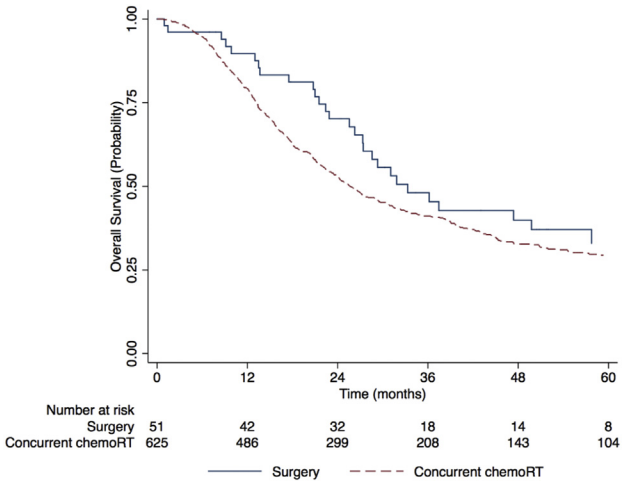

Fig 5. Overall survival of cT1–3 N1 M0 small cell lung cancer (SCLC) patients with no comorbidities, stratified by surgery versus concurrent chemoradiation. (CI = confidence interval; RT = radiation.)

Since these trials, however, there have been many developments in SCLC therapy [13, 14]. For example, etoposide and cisplatin have replaced alkylator/anthracycline-based regimens because of their superiority in both efficacy and toxicity for limited-stage SCLC [8]. Radiation given concurrently with chemotherapy has been shown to improve survival over sequential administration for SCLC [8, 13–15]. There have also been newer staging modalities for SCLC which more accurately select the appropriate patients for possible resection [8]. Our study findings suggest that in the setting of these contemporary therapeutic options, surgery with adjuvant chemotherapy with or without radiation as a viable option for the treatment of node-positive SCLC needs to be considered and further studied in randomized trials.

One important limitation to this study is that we do not know the specific reason as to why a patient underwent surgery for N1 SCLC in the surgical cohort. Most likely, given that the current standard of care is chemoradiation and not surgery for N1 SCLC, most of the patients in the surgery group had a nondefinitive preoperative pathologic diagnosis or a misdiagnosis before their operation and that the finding of SCLC was a surprise or unexpected. Of note, it has been previously reported that SCLC can be misinterpreted as a lower-grade neuroendocrine pulmonary tumor (typical or atypical carcinoid), as non-SCLC (eg, as large cell neuroendocrine carcinoma), or as neuroendocrine "not otherwise specified" [16].

There are several other limitations to this study. First, it is a retrospective study, and some confounding variables

may not have been accounted for in the analysis. The NCDB does not have data on the number of doses of chemotherapy administered, the specific chemotherapy agents and types of radiation administered, local and distant recurrence and disease-free survival, and performance status of patients at different time points. Second, there is a possibility that patients in the chemoradiation group were sicker than patients in the surgical group. We attempted to minimize this bias by including the CDCC index as a covariate in the Cox models. We also performed a separate analysis limited to patients who had no comorbidities and found that there was a trend toward improved survival in the surgical group compared with the concurrent chemoradiation group, although the association was not statistically significant. It is possible that the loss of significance for the surgery group was due to a loss of statistical power. Third, the NCDB does not have data on how clinical N1 disease was detected. In addition, the NCDB does not provide details about extent of N1 disease; thus, we were unable to distinguish between microscopic and bulky N1 disease. It is possible that bulky N1 disease may have been more common in the chemoradiation group, which may have biased results in favor of the surgery group. Finally, the surgery group included sublobar resections, which have been shown to be oncologically inferior operations to lobectomy for SCLC [17]. Although we only included curative-intent (nonpalliative) surgical resections in this study, we do not know for certain how many of the patients underwent a wedge resection, were found to have SCLC on frozen section, and then referred directly to chemotherapy with or without radiation without proceeding to lobectomy. By including nonanatomic resections in the surgery group, we may have underestimated the impact of surgery for patients with T1–3 N1 M0 SCLC.

In conclusion, in an analysis of a population-based data set, surgery with adjuvant chemotherapy with or without radiation therapy was associated with better survival than concurrent chemoradiation for T1–3 N1 M0 SCLC. Because of the limitations of the NCDB, this study does not demonstrate that surgery is superior to concurrent chemoradiation for T1–3 N1 M0 SCLC, but it does show that selected patients who undergo surgery for N1 SCLC have reasonable long-term outcomes. These results support the re-evaluation of the role of surgery in multimodality therapy for N1 SCLC in a clinical trial setting.

The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer accredited hospitals. The data used in the study are derived from a de-identified 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 investigators. This work was supported by the National Institutes of Health Cardiothoracic Surgical Trials Network (B.C.G. and M.G.H.), Grant No. 5U01HL088953-05, and the American College of Surgeons Resident Research Scholarship (C.J.Y.).

References

1. Lad T, Piantadosi S, Thomas P, Payne D, Ruckdeschel J, Giaccone G. 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–3S.
2. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. Lancet 1973;2:63–5.
3. Inoue M, Miyoshi S, Yasumitsu T, et al. Surgical results for small cell lung cancer based on the new TNM staging system. Thoracic Surgery Study Group of Osaka University, Osaka, Japan. Ann Thorac Surg 2000;70:1615–9.
4. Rostad H, Naalsund A, Jacobsen R, et al. Small cell lung cancer in Norway. Should more patients have been offered surgical therapy? Eur J Cardiothorac Surg 2004;26:782–6.
5. 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.
6. Lim E, Belcher E, Yap YK, Nicholson AG, Goldstraw P. The role of surgery in the treatment of limited disease small cell lung cancer: time to reevaluate. J Thorac Oncol 2008;3:1267–71.
7. Schneider BJ, Saxena A, Downey RJ. Surgery for early-stage small cell lung cancer. J Natl Compr Canc Netw 2011;9:1132–9.
8. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer (version 2.2015). Fort Washington, PA: National Comprehensive Cancer Network; 2015.
9. Sher DJ, Liptay MJ, Fidler MJ. Prevalence and predictors of neoadjuvant therapy for stage IIIA non-small cell lung cancer in the National Cancer Database: importance of socioeconomic status and treating institution. Int J Radiat Oncol Biol Phys 2014;89:303–12.
10. American Joint Committee on Cancer In: Green FL, Page DL, et al (eds). AJCC Cancer Staging Manual. 6th ed. New York: Springer; 2002.
11. American College of Surgeons Commission on Cancer: Cancer Program Standards 2012: Ensuring Patient-Centered Care. Chicago, IL: American College of Surgeons; 2012.
12. Yang CJ, Kumar A, Gulack BC, et al. Long-term outcomes after lobectomy for non-small cell lung cancer when unsuspected pN2 disease is found: A National Cancer Data Base analysis. J Thorac Cardiovasc Surg 2016;151:1380–8.
13. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 2002;20:3054–60.
14. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol 2004;22:4837–45.
15. Pijls-Johannesma M, De Ruysscher D, Vansteenkiste J, Kester A, Rutten I, Lambin P. Timing of chest radiotherapy in patients with limited stage small cell lung cancer: a systematic review and meta-analysis of randomised controlled trials. Cancer Treat Rev 2007;33:461–73.
16. Nicholson SA, Beasley MB, Brambilla E, et al. Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens. Am J Surg Pathol 2002;26:1184–97.
17. Combs SE, Hancock JG, Boffa DJ, Decker RH, Detterbeck FC, Kim AW. Bolstering the case for lobectomy in stages I, II, and IIIA small-cell lung cancer using the National Cancer Data Base. J Thorac Oncol 2015;10:316–23.