Editorial

Under-treatment of small cell lung cancer: the case for surgical resection

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Limited stage (LS) small cell lung cancer (SCLC) has traditionally been treated with chemoradiation but the potential role of surgical treatment in early stage disease remains a topic of debate. An analysis published in *Lung Cancer* in May 2017 by Wakeam *et al.* presents the argument that selected patients with early stage SCLC may benefit from surgical resection (1).

The authors present a retrospective cohort analysis of the National Cancer Database (NCDB) in which they formed propensity-matched cohorts of patients with early stage SCLC who were treated with and without surgical resection. They subsequently compared overall survival (OS) between these cohorts. The study population was limited to patients diagnosed between 2004 and 2013 with clinical stages I to IIIA based on the 7th edition of AJCC's tumor, node, metastases (TNM) staging criteria. Pathologic confirmation of invasive SCLC was required for inclusion. The authors first compared survival between patients who underwent surgical resection and those who did not, stratified by stage. Next, the authors selected only healthy patients with clinical stage I or II disease (highly select cohort) and compared survival between patients who underwent standard-of-care chemoradiation therapy and patients who underwent lobectomy plus adjuvant chemotherapy (and radiation therapy if the patient was found to have nodal disease on pathologic review) .

Surgery was associated with longer survival in all cohorts and provided the greatest survival benefit for patients with stage I (median OS, 38.6 *vs.* 22.9 months; HR, 0.62; 96% CI: 0.57–0.69, P<0.0001) and T1–T2 N0 tumors (median OS, 40.1 months; 95% CI: 35.4–45.0 *vs.* 23.0, 95% CI: 21.3–24.3, P<0.0001). The difference in survival for patients with stage II disease was not statistically significant. Of note, 35% of patients in the surgical cohort did not receive chemotherapy; the reason for this deviation from recommended care is unclear from the data available and should be investigated in future studies.

To assess operative factors associated with survival, the authors used Cox proportional hazards models. From these, the authors concluded that obtaining an R0 resection was necessary to see a survival benefit from surgery (HR, 0.59; 95% CI: 0.54–0.66 for R0 as compared to non-surgical treatment; HR for R1 and R2 resection did not differ statistically from nonsurgical therapy). These results were robust to sensitivity analysis assessing the possibility of an unmeasured confounder. In the highly select cohort, surgical therapy with adjuvant chemotherapy (and radiation if pathologically found to have nodal disease) was associated with significantly longer survival when compared to chemoradiation alone (48.6 months, 95% CI: 40.7–59.1

months, P<0.0001 *vs.* median OS 28.7 months, 95% CI: 24.6–32.7).

SCLC currently makes up 13% of all lung cancer diagnoses (2). This disease is characterized by early distant metastases, high response rate to chemoradiation therapy, but an almost universal relapse rate leading to an overall 5-year survival of <7% (3). Clinically, most patients are diagnosed at an advanced age (>70 years old), and are former or current smokers. The incidence of SCLC in the US has decreased in recent years, mirroring the decline in tobacco use nationwide. However, there are still an estimated 31,000 cases for annually (3).

Traditionally, staging of SCLC was based on the 1950s Veterans' Administration Lung Study Group's criteria: LS referred to tumor that was localized to a hemithorax (specifically, within one radiation portal), whereas extensive stage (ES) referred to disease that had spread beyond a single radiation portal (and thus would include any distant metastasis as well as a malignant pleural effusion). Subsequently, in 1989, the International Association for the Study of Lung Cancer (IASLC) recommended expanding the definition of LS to include tumors with nodal metastasis to the ipsilateral and contralateral hilum, as well as ipsilateral and contralateral supraclavicular nodal basins. The goal of this revised staging criteria was primarily to guide the treatment decision between chemoradiation (for LS) and chemotherapy alone (for ES). However, based on retrospective, observational studies indicating that surgery may be beneficial for very early stage SCLC, some clinicians advocated a transition to a TNM staging system. A validation study suggested that TNM staging may more accurately predict survival in SCLC, especially for T1 versus all other T stages, between N0/1 and N2/3 disease, as well as between N1 and N2 (4).

Historically, all lung cancer was treated with surgical resection where possible. This axiom held true until 1973 when a clinical trial was published comparing surgery to radiation therapy for SCLC (5). This study showed a significantly worse survival for patients treated with surgical resection alone. After this time, SCLC has been thought of as a non-surgical disease. However, multiple factors limit the application of these findings to today's practice. First, modern staging technology (positron emission tomography, navigational bronchoscopy, endobronchial ultrasound, mediastinoscopy, etc.) allows better identification of patients with LS disease. Second, the surgical techniques have evolved: 48% of patients in the 1969 trial underwent a pneumonectomy via an open thoracotomy. Finally, the study did not include patients with T1–2 N0 disease whom we now know most benefit from surgery (6).

While there are no recent randomized controlled trials (RCTs) of acceptable quality evaluating the use of surgery for early stage SCLC (7), large database studies have suggested that there may be a survival benefit to surgical resection (8-12). These findings have supported the current inclusion of surgical therapy in the National Cancer Care Network (NCCN) guidelines for early stage SCLC. Surgery is recommended only for T1–2 N0 disease and should be performed only after clinical evaluation for distant metastasis and pathologic evaluation of the mediastinum for nodal disease. The article under discussion further supports the use of surgery for early-stage SCLC.

Although RCTs are considered the top level of evidence by most hierarchies, this study design may not be feasible to evaluate the role of surgery in SCLC for two major reasons. First, the rarity of the disease: node-negative, localized tumors make up a small minority of all SCLC, a histology which itself makes up a small minority of all lung cancers. Accruing the number of patients needed to ensure adequate power would require multiple sites and a long recruitment period. Second, patient willingness to be randomized to one of two very disparate treatments (e.g., surgery and chemoradiation) is often less than between similar treatments (e.g., different chemotherapy regimens). The difficulty in patient recruitment to surgical trials is highlighted by the trials for NSCLC and acute appendicitis (13,14).

For these reasons, the time required to plan a RCT and recruit from a limited patient pool may exceed the time it takes for new surgical, medical, and radiation technology to evolve. Finally, the lack of a surgically oriented clinical trials network following the dissolution of ACOSOG has further increased the difficulty in obtaining support for surgery-intensive clinical trials. In this setting, comparative effectiveness research of available, prospectively collected, observational data must inform our practice. To ensure that their analysis approximated randomization as closely as possible, the authors used propensity score matching to account for selection bias.

As mentioned, this article has many strengths. Chief among these is the data source; the NCDB is estimated to include greater than 80% of all lung cancer diagnoses in the United States (15). The data is abstracted by trained clinical reviewers and is audited for accuracy. The database contains detailed information about the diagnosis, staging, and treatment for each patient. Additionally, patients are followed for OS. The Public Use File is then de-identified which,

Table 1 Outcomes after surgery (S+) *vs.* no surgery (S–) for small cell lung cancer

Publication	Data source	Patient population	Median survival (months)	% 5-yr OS
Wakeam 2017	NCDB	Stage I–IIIA	S+ 32.4, S– 20.2	NR
	NCDB	T1–T2, N0	S+ 40.1, S– 23.0	NR
Yang 2017	NCDB	T1–T2, N0	S+ 54.4, S– 30.5	S+ 47.6, S– 29.8
Varlotto 2011	SEER	Stage I*	Lobe 50, SLR 30, S– 20	Lobe 47.4, SLR 28.5, S– 17.2
Schreiber 2010	SEER	T1–T4 Nx–N2	S+ 28, S– 13	S+ 53, S– 32
Weksler 2012	SEER	Stage I–II	S+ 34, S– 16	NR
Gaspar 2012	NCDB	Stage I–II†	S+ 30.8, S– 15.0	NR
	NCDB	Stage III†	S+ 16.5, S– 11.9	NR

*, outcomes reported for stage I patients only; †, outcomes reported for stage I–II patients reported separately from stage III patients. NCDB, National Cancer Database; SEER, Surveillance, Epidemiology, and End Results; OS, overall survival; NR, not reported; S+, surgery cohort; S–, non-surgical cohort; SLR, sub-lobar resection.

in addition to removing other details, aggregates medical comorbidities into categories based on Charlson-Deyo modified comorbidity scale. However, the patient level data available in the NCDB exceeds that in the SEER registry, which includes only a sample of the US population (16).

Second, the statistical methodology is robust. While observational studies are subject to confounding bias, potentially resulting in incorrect estimates of treatment effects, the use of propensity scoring helps address this issue (17). The score can be used in multiple ways: as an additional covariate in a multivariable model, as a method for stratification of cohorts, or to create matched cohorts. The key assumption in this statistical method is that there is no unmeasured covariate present that is unaccounted for in the scoring model. The dataset the authors used lacks important variables determining suitability for surgery (e.g., performance status, pulmonary function tests, and smoking status). However, to assess whether the presence of one of these or another unmeasured covariate might have qualitatively affected the results of the analysis, the authors completed a sensitivity analysis demonstrating that their results are robust to an unmeasured confounder so long as it increases the odds of exposure (to a particular treatment) by less than 40%.

The inherent weaknesses of large database analyses should also be mentioned. First, the authors chose to include all possibly operable patients instead of limiting the sample to those for whom guidelines currently endorse surgery. The data for such a heterogeneous group should be interpreted carefully. While the results showed that surgery may have the most beneficial effect for patients with T1–T2N0 disease, it is important to look at all patients who did in fact undergo surgery for their disease to understand what effect surgery may have for this cohort. The authors addressed this concern by stratifying the survival curves by stage, although survival for these cohorts were not compared to the current standard-of-care non-operative therapy. To address this additional concern, the authors created a highly select cohort for whom they compared survival after surgery to a non-operative cohort who had received the current standard of concurrent multi-agent chemotherapy and radiation at a dose of greater than 40 cGy. Surgery appeared to provide a survival advantage over maximum medical therapy in this selected cohort of stage I and II SCLC patients.

A second weakness of this analysis is the choice of defining stage. In the NCDB, both clinical and pathologic stage are available, and they are frequently discordant. While the authors do not specify which was used preferentially for survival analysis, only clinical stage is reported in *Table 1*, suggesting that this was used to determine stage classifications. Using clinical stage is ideal for assessing the propensity score (because the determination of therapy will be made prior to availability of final pathology), but for analyzing survival data, pathologic stage might be more appropriate. The non-surgical group may have falsely lower survival outcomes for each stage because up to 25% of patients treated with chemoradiation could have been upstaged if mediastinal staging was performed (18).

A final minor weakness of the analysis is the propensity matching process itself. While the authors report an analysis assessing for the presence of an unknown confounder, they did not report any sensitivity analysis of the matching process. There are multiple decisions made during a propensity-matching analysis (e.g., caliper distance, matching ratio, replacement, and method of statistical

analysis), each of which could have substantial effects on the final results and conclusion.

This article contributes to the available data for surgery in SCLC (*Table 1*). Yang *et al.* recently published a retrospective analysis of the NCDB focusing on patients diagnosed from 2003–2011 with T1–T2 N0 SCLC (12). The authors compared OS between two propensity-matched cohorts: patients treated with surgery and adjuvant chemotherapy versus those treated with concurrent chemoradiation alone. In this propensity matched cohort, the authors found improvement in median survival for surgically treated patients (54.4 *vs.* 30.5 months; P<0.01). The results reported are similar to those reported by Dr. Wakeam *et al.* [median survival for T1–T2, N0 patients only: 40.1 months for surgical cohort versus 23.0 months for the nonsurgical cohort; appendix 5 (1)].

Although these data may shed light on the debate between surgery and non-operative management for SCLC, another important aspect of treatment is whether adjuvant therapies should be offered after surgical resection. In Wakeam's analysis, the highly select cohort compared maximum medical therapy to resected patients treated with adjuvant chemo- and radiotherapy. Although it was not a primary objective of the analysis, the authors report an improved hazard ratio for patients treated with surgery and adjuvant therapy of any kind (HR, 0.78; 95% CI: 0.68–0.92) as compared to surgery alone (HR, 0.57; 95% CI: 0.52–0.64).

To examine the utility of radiation therapy after surgical resection, Varlotto *et al.* performed a retrospective analysis of SEER data to evaluate survival in stage I and II SCLC treated with surgery alone, radiation alone, or surgery and radiation (9). In this study, patients treated with surgery alone had longer median survival as compared to patients treated with radiation alone (50 months for lobar resection, 30 months for sublobar, and 20 months for radiation). Moreover, the addition of radiation therapy to surgery had no significant effect on survival.

Yang *et al.* performed a retrospective analysis of the NCDB to evaluate the benefit of adjuvant chemotherapy in a cohort of patients who had undergone surgical resection for SCLC (19). They found that patients treated with surgery alone had worse OS when compared to patients who underwent adjuvant chemotherapy alone (HR, 0.78; 95% CI: 0.63–0.95) or adjuvant chemotherapy plus cranial radiation (HR, 0.52; 95% CI: 0.36–0.75).

In conclusion, the analysis by Wakeam *et al.* provides additional evidence in support of surgical resection for early SCLC, especially T1–T2 N0 disease. Future research may include analyses focused on more discrete patient populations or, as Wakeam *et al.* advocate, a RCT to define the role of tri-modality therapy. While LS and ES terminology was historically used to classify SCLC, more accurate staging nomenclature is necessary to continue to study treatment modalities in these discrete patient populations where surgery may afford a benefit. For this reason, we advocate for the use of TNM staging for all SCLC. And second, surgeons should maintain an active role in the multidisciplinary management of earlier stage SCLC and in the design, implementation, and analysis of RCTs for patients in whom surgery may be an option.

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Footnote

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