Editorial

Optimal local therapy for early-stage small cell lung cancer: surgery needs a seat at the table

Kathryn E. Engelhardt[1,2], David D. Odell[1,3,4], Malcolm M. DeCamp[3,4]

[1]Department of Surgery and Center for Healthcare Studies, Surgical Outcomes and Quality Improvement Center, Feinberg School of Medicine, Northwestern University Feinberg School of Medicine, Chicago, USA; [2]Department of Surgery, Medical University of South Carolina, Charleston, South Carolina, USA; [3]Division of Thoracic Surgery, [4]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, USA

Correspondence to: Malcolm M. DeCamp, MD. Division of Thoracic Surgery, Northwestern University Feinberg School of Medicine, Northwestern Memorial Hospital, 676 North Saint Clair Street, Suite 650, Chicago, Illinois 60611, USA. Email: mdecamp@nm.org.

Comment on: Yang CJ, Chan DY, Shah SA, *et al.* Long-term Survival After Surgery Compared With Concurrent Chemoradiation for Node-negative Small Cell Lung Cancer. Ann Surg 2017. [Epub ahead of print].

Submitted Sep 13, 2017. Accepted for publication Sep 19, 2017.
doi: 10.21037/tcr.2017.09.41
View this article at: http://dx.doi.org/10.21037/tcr.2017.09.41

The National Comprehensive Cancer Network (NCCN) guidelines, in addition to other international societies, recommend surgery for American Joint Committee on Cancer clinical stage I small cell lung cancer (SCLC) after a careful radiographic evaluation excludes distant metastases and invasive mediastinal staging excludes nodal disease. However, the data to support these guidelines are limited and therefore it is suspected that these guidelines are not universally followed (1). Yang and colleagues recently published their analysis of data from the National Cancer Database (NCDB) comparing overall survival (OS) in patients with cT1-2N0M0 SCLC who underwent surgery with adjuvant chemotherapy with or without adjuvant radiation therapy to OS in those treated with only concurrent chemoradiation (2).

The authors performed a retrospective cohort analysis of the NCDB Public Use File in an attempt to meaningfully assess the impact of surgical treatment on survival. They included all patients diagnosed with SCLC from 2003–2011, excluding, for example, patients with missing treatment data or those treated with palliative intent (See Figure 1 in Yang 2017). Surgical patients were treated with resection (wedge, sublobar, lobectomy, or pneumonectomy) within 30 days of diagnosis followed by adjuvant chemotherapy. Nonsurgical patients received chemotherapy and concurrent radiation, defined as radiation commencing within 10 weeks of diagnosis, in order to exclude patients likely treated for recurrence rather than prophylaxis. No specifics regarding the chemotherapy regimen (e.g., agent, cycles, etc.) were available from the dataset.

These cohorts formed the basis for all subsequent survival analyses. The authors first compared unadjusted OS for the entire cohort and next did an adjusted analysis to identify factors associated with OS. They then created a matched cohort and compared OS having accounted for referral bias. To further account for confounding bias, the authors limited their matched cohort to "healthy" patients (Charlson-Deyo Comorbidity score of zero) and repeated the survival analysis. Lastly, they identified factors associated with OS in the surgical cohort.

The analytic cohort included 2,301 patients. As expected, the majority 1,620 (70.4%) received chemoradiation and only 681 (29.6%) underwent surgery. In unadjusted analysis, patients undergoing surgery had significantly better 5-year OS than those who did not (48.1% *vs.* 28.3%; P<0.01). Surgery was associated with improved survival (HR 0.61; 95% CI: 0.53–0.71; P<0.01) in the adjusted analysis as well. After propensity-score matching for patient, tumor, and facility characteristics, 501 patients remained in each treatment cohort. In this matched cohort, 5-year OS remained significantly better in the surgery group both for the overall cohort (47.6% *vs.* 29.8%; P<0.01) and the "healthy" subgroup (49.2% *vs.* 32.5%; P<0.01). Finally, the authors found that decreased age (HR for age as a continuous variable 1.03; 95% CI: 1.01–1.04; P<0.01) and lobectomy (HR as compared to wedge resection 0.71; 95% CI: 0.55–0.92; P=0.01) were associated with improved survival among patients who had undergone surgery.

Lung cancer is the leading cause of cancer related death in the United States with SCLC representing 13% of these diagnoses (3). Distant metastases are common at the time of diagnosis or in the early phases of disease management. Despite the high initial response rate to chemoradiation therapy, the disease has an almost universal relapse rate leading to an overall 5-year survival of <7% (4). Clinically, most patients are diagnosed at an advanced age (>70 years old), and are former or current smokers. As tobacco use has declined nationwide, so too has the incidence of SCLC in the US. However, there are still an estimated 31,000 cases annually (4).

Until 1973 all lung cancer was treated with surgical resection where possible. That treatment paradigm changed when Fox and colleagues published a clinical trial comparing surgery to radiation therapy for SCLC (5). Patients in this trial who were treated with surgical resection had significantly worse survival than those treated with radiation. This practice-changing article created the perception of SCLC as a non-surgical disease. However, much has changed in the fields of pulmonology, radiation oncology, medical oncology, and thoracic surgery since 1973. One important paradigm shift has been the development of modern staging technologies (positron emission tomography, navigational bronchoscopy, endobronchial ultrasound, mediastinoscopy, etc.) which allow better identification of patients with limited stage disease. Further, surgical techniques have evolved: 48% of patients in the 1969 trial underwent a pneumonectomy via an open thoracotomy. Because of these advances, the findings from that 1973 trial are no longer relevant in modern medical practice. Moreover, the Fox study did not include patients with T1-2 N0 disease whom we now know most benefit from surgery (6).

The NCCN recommends surgery, preferable lobectomy for T1-2N0M0 disease and only after thorough evaluation for distant metastasis as well as invasive staging of the mediastinum to exclude nodal disease. Level I evidence in support of these guidelines is nonexistent (1), however some large database studies have suggested that there may be a survival benefit to surgical resection (7-11). In this most recent publication, Yang and colleagues add to the evidence in support of surgery for early-stage SCLC.

Although NCCN guidelines do currently recommend surgery for early stage, node-negative disease, Yang and colleague's findings suggest surgery is being underutilized in this population. This may be due to a lack of high quality evidence supporting improved survival after surgery or the lack of surgical input into multidisciplinary treatment planning. The randomized controlled trials completed to date which have compared surgery to non-surgical treatment for SCLC are over forty years old and included heterogeneous patient populations; node-positive patients made up the majority of the surgical cohort in these early trials (5,12). More recently published large database analyses have been similarly limited by inadequate treatment data in the nonsurgical cohorts (6,13,14). Yang and colleagues addressed these concerns both by limiting their patient population to those who are most likely to benefit from surgical resection, and by only including nonsurgical patients who were treated with standard of care maximum medical therapy.

This article has many strengths, chief of which 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, in addition to removing other details, aggregates medical comorbidities into categories based on Charlson-Deyo modified comorbidity scale (16). However, the patient level data available in the NCDB exceeds that in the SEER registry, which includes only a sample of the US population and lacks any data concerning chemotherapy (17).

This article is unique from previous literature in that the authors limited the patient sample to a homogeneous patient cohort. They further limited a subset analysis to only "healthy" patients, similar to a recent analysis for early state non-small cell lung cancer patients (18). A major criticism of all retrospective analyses is an inability to account for confounding. However, limiting the patient sample, in addition to propensity-score matching and regression models, is an effective method of accounting for possible confounding bias (19).

This study has some minor weaknesses which are intrinsic to the data source which should be mentioned.

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

Publication	Data source	Patient population	Median survival (months)	% 5-yr OS
Wakeam 2017	NCDB	Stage I–IIIA	S+ 32.4; S– 20.2	NR
Wakeam 2017	NCDB	T1–T2 N0	S+ 40.1; S– 23.0	NR
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

*, outcomes reported for stage I patients only; NCDB, national cancer database; SEER, surveillance, epidemiology, and end results; OS, overall survival; NR, not reported; Lobe, lobectomy; SLR, sub-lobar resection.

Comorbidities in the NCDB are collected by clinical abstractors through a retrospective review process. These comorbidities are then converted into an overall score, the Charlson-Deyo Comorbidity index score, for public reporting purposes. However, the initial abstraction is based on clinical documentation and thus is only as accurate as the physician documentation of comorbid conditions, which frequently contains inaccuracies (20). In this manuscript, problems arising from reliance on the Charlson-Deyo Comorbidity score in the NCDB to account for medical comorbidities are subtly revealed. For one, in the unadjusted analysis, patients receiving concurrent chemoradiation were more likely to have fewer comorbidities. Additionally, in the multivariable logistic regression analyzing predictors of surgery, patients with 1 or 2+ comorbidities were two times as likely to have undergone surgery as compared to patients with zero comorbidities. Both of these findings are contrary to what might be hypothesized.

It is not clear from the presented data why patients with more comorbidities were more likely to have undergone surgery. One hypothesis is that surgery patients, rather than actually having more medical problems than non-surgical patients, simply have more of these comorbid conditions documented. Patients who are hospitalized, such as following surgery, are more likely to have more comorbidities documented than patients seen in the outpatient setting due to the larger volume medical record (21,22). Patients treated with surgery are much more likely to have been admitted for that treatment when compared to patients treated with radiation and chemotherapy; both of which are outpatient treatments for SCLC. Thus, it follows that the NCDB may be capturing more data about comorbid conditions for surgical patients than it does for non-surgical patients. If this is the case, limiting an analysis to only those patients with Charlson-Deyo Comorbidity score scores equal to zero may introduce bias because the nonsurgical cohort may include undocumented comorbid conditions. Again, it is unclear if these hypotheses are accurate but this is an important consideration for any NCDB analysis.

This article supplements the available data supporting the use of surgery for early stage SCLC (*Table 1*). Wakeam *et al.* recently published a retrospective propensity-matched cohort analysis of data also utilizing data from the NCDB in which they examined the survival benefit of surgery for stages I to IIIA SCLC (11). Unlike the analysis by Yang *et al.*, their analysis is limited by heterogeneity: the authors included a wider range of stages, nodal status, and adjuvant treatment. In fact, up to 35% of their surgical cohort did not receive any chemotherapy.

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 (8). 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. In their multivariable analysis, lobectomy without radiotherapy was an independent predictor of improved OS.

In conclusion, the analysis by Yang *et al.* provides additional support for surgery as the optimal local therapy for node-negative SCLC. This contemporary report also highlights the under treatment of early stage disease as only 30% of stage-eligible patients underwent surgery. Future research aimed at understanding and addressing this quality gap would ensure patients receive care that is not only guideline-concordant but also offers a significant survival benefit. In order to further confirm these findings, more granular data is needed regarding medical comorbidities, performance status, and pulmonary function tests. Feasibility of including these variables in the NCDB should be explored. Quality therapeutic decision making for patients with limited stage SCLC has always required multidisciplinary expertise. Thoracic surgeons deserve a seat at the table.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Wei Xu (Jiangsu Provincial Key Laboratory of Geriatrics, Department of Geriatrics, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.09.41). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Barnes H, See K, Barnett S, et al. Surgery for limited-stage small-cell lung cancer. Cochrane Database Syst Rev 2017;4:CD011917.
2. Yang CJ, Chan DY, Shah SA, et al. Long-term Survival After Surgery Compared With Concurrent Chemoradiation for Node-negative Small Cell Lung Cancer. Ann Surg 2017. [Epub ahead of print].
3. Bernhardt EB, Jalal SI. Small Cell Lung Cancer. In: Reckamp KL. editor. Lung Cancer: Treatment and Research. Cham: Springer International Publishing, 2016:301-22.
4. Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? Cancer 2015;121:664-72.
5. 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.
6. 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.
7. 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;116:1350-7.
8. Varlotto JM, Recht A, Flickinger JC, et al. Lobectomy leads to optimal survival in early-stage small cell lung cancer: a retrospective analysis. J Thorac Cardiovasc Surg 2011;142:538-46.
9. Weksler B, Nason KS, Shende M, et al. Surgical resection should be considered for stage I and II small cell carcinoma of the lung. Ann Thorac Surg 2012;94:889-93.
10. Gaspar LE, McNamara EJ, Gay EG, et al. Small-cell lung cancer: prognostic factors and changing treatment over 15 years. Clin Lung Cancer 2012;13:115-22.
11. Wakeam E, Acuna SA, Leighl NB, et al. Surgery Versus Chemotherapy and Radiotherapy For Early and Locally Advanced Small Cell Lung Cancer: A Propensity-Matched Analysis of Survival. Lung Cancer 2017;109:78-88.
12. 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-3S.
13. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. J Thorac Oncol 2007;2:1067-77.

14. de Hoyos A, DeCamp MM. Surgery for small cell lung cancer. Thorac Surg Clin 2014;24:399-409.
15. Bilimoria KY, Stewart AK, Winchester DP, et al. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol 2008;15:683-90.
16. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.
17. Katz SJ. Cancer Care Delivery Research and the National Cancer Institute SEER Program: Challenges and Opportunities. JAMA Oncol 2015;1:677-8.
18. Rosen JE, Salazar MC, Wang Z, et al. Lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer. J Thorac Cardiovasc Surg 2016;152:44-54.e9.
19. Pourhoseingholi MA, Baghestani AR, Vahedi M. How to control confounding effects by statistical analysis. Gastroenterol Hepatol Bed Bench 2012 Spring;5:79-83.
20. Frazee RC, Matejicka AV 2nd, Abernathy SW, et al. Concurrent chart review provides more accurate documentation and increased calculated case mix index, severity of illness, and risk of mortality. J Am Coll Surg 2015;220:652-6.
21. Baldwin LM, Klabunde CN, Green P, et al. In search of the perfect comorbidity measure for use with administrative claims data: does it exist? Med Care 2006;44:745-53.
22. Mnatzaganian G, Ryan P, Norman PE, et al. Accuracy of hospital morbidity data and the performance of comorbidity scores as predictors of mortality. J Clin Epidemiol 2012;65:107-15.

Cite this article as: Engelhardt KE, Odell DD, DeCamp MM. Optimal local therapy for early-stage small cell lung cancer: surgery needs a seat at the table. Transl Cancer Res 2017;6(Suppl 7):S1248-S1252. doi: 10.21037/tcr.2017.09.41