

Surgery for small cell lung cancer in the modern era: opportunities and challenges

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This issue of the *Journal of Thoracic Diseases* includes two well-written perspective pieces on our recent examination of surgery for early and locoregionally advanced small cell lung cancer (SCLC) (1,2). Our study found that surgical resection was associated with longer survival despite stage-specific propensity matching that accounted for patient, tumor and hospital characteristics (3). The two editorials provide contrasting views on our results, and both make interesting observations and criticisms. The controversy around the use of surgery in early and locoregionally advanced SCLC has little chance of being resolved in the near future, although there are purportedly ongoing randomized clinical trials in Germany and Asia which may answer many of the questions that exist about the role of surgery today (4).

In their editorial, Ernani and Ganti (rightly) caution the over-interpretation of retrospective evidence, and point to existing randomized evidence from over a generation ago that supports omitting surgery in the treatment of these patients. However, in the absence of high quality randomized evidence from the modern era, what options do clinicians have to guide their decisions? For the patient in our clinic today, should we rely on the Medical Research Council Trial (5), performed in the 1960's and 1970's when staging was accomplished with an X-ray and most surgical patients underwent a pneumonectomy? The trial published in the 1990's by Lad *et al.* (6), specifically excluded small peripheral lesions, which are the majority of those for

whom we might consider surgery in the modern era. Hence, retrospective evidence, with all its known limitations, may be all that exists to guide our decisions. Making decisions in multidisciplinary groups, and not in a vacuum—groups that should include dedicated thoracic surgeons—is that much more important given the state of the evidence.

One commonality between the reviews is a criticism of the use of clinical staging to perform the matching. However, patients are selected for definitive chemoradiotherapy largely on the basis of clinical stage, and hence comparisons between surgery and chemoradiotherapy must use clinical stage for a valid comparison. In an accompanying investigation we examined practice patterns for cT1/T2N0 SCLC patients and found that only 7% of non-operative patients underwent invasive pathologic staging of their mediastinum (7). Further, the National Cancer Database (NCDB) contains pathologic stage, but it is not possible to determine whether pathologic nodal staging was known preoperatively (as it would be if the patient had undergone mediastinoscopy or endobronchial ultrasound-guided fine needle aspiration). Hence for the purposes of our study, using pathological staging was practically not possible and given that most decisions for the non-operative patients are made based on clinical grounds alone, this is a necessary strategy for comparison. As Ernani and Ganti note, almost 30% of the IIIA patients are in fact downstaged with surgery, which is consistent with reports from the International Association for the Study of Lung Cancer SCLC database (8). While an astute observation, the

validity of their assertion that this nullifies the comparisons that were made is not clear. If appropriate invasive mediastinal staging of the non-operative patients were carried out, is it not fair to assume that many of these patients would also be downstaged? This, does, however, make a compelling argument for aggressive mediastinal staging and pathologic nodal evaluation, either by endobronchial ultrasound fine-needle aspiration or mediastinoscopy, to identify potential surgical patients and more accurately stratify prognosis in patients with clinical stage IIIA disease. It may also be helpful for radiation oncologists in making decisions about patient selection for stereotactic body radiation therapy (SBRT) versus conventional radiotherapy techniques (9). Furthermore, it underscores the importance of moving away from the Veteran's Administration categorization system for SCLC and moving toward the widespread use of the TNM system both for more accurate prognostication and greater clarity in therapeutic decision making (8).

A further criticism leveled at the study was that we examined patients in the main cohorts who underwent treatment that was less than the standard of care. While it is true that a minority of patients received chemotherapy without radiotherapy, many surgical patients also received lesser resections (i.e., wedge resections) which are known to be inferior. Unlike a clinical trial, an advantage of large database research is that it can demonstrate 'real world' trends in practice. The finding that many patients with SCLC do not receive guideline-concordant care—whether operative or non-operative—is a notable finding in and of itself. This concern also prompted the conduct of what was termed the "highly selected" analysis, where patients without comorbidity with stages I and II disease receiving lobectomy and adjuvant chemotherapy (and radiotherapy in node-positive patients) were compared to those receiving high-dose concurrent chemoradiotherapy. This analysis confirmed a nearly 2-year longer survival in the surgical group. A survival difference of this magnitude, if confirmed in a randomized trial, would be a breakthrough in the treatment of SCLC.

What challenges remain in assuring proper treatment for these patients? Many patients undergo resection for diagnostic purposes (i.e., a non-anatomic wedge) and this may represent a window that can be used for quality improvement and intervention. Surgeons will need to be educated on the value of staging the mediastinum for accurate prognostication and to determine the patient's need for further radiation to the mediastinum, and to consider completion lobectomy (10). Convincing medical, radiation and surgical oncologists of

the value of surgery for lobar control and long-term survival in this disease is perhaps a greater challenge—reflected in the fact that only 1 in 3 patients with early (T1 and T2N0) disease is even referred for surgical consultation (7). However, with high rates of local recurrence, even with modern chemoradiotherapeutic techniques (11), surgical control of the primary tumor may improve overall and disease-free survival. Knowledge translation and regionalization strategies may be great opportunities for quality improvement in this population, but in the absence of a definitive randomized trial showing that surgery improves outcomes, these challenges will surely persist.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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