Editorial

Viewing the big picture on small cell lung cancer

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The use of chemotherapy, radiation therapy, and surgery are all part of the treatment toolbox used to treat patients with small cell lung cancer (SCLC). Opinions regarding the best treatment strategy remain varied and are limited by the available high-level data surrounding SCLC. We, therefore, commend Wakeam and colleagues (1) for the first of its kind, propensity matched retrospective study of the National Cancer Database (NCDB) comparing outcomes of resected stage I–IIIA SCLC. Their investigation fills two critical areas of void in the current literature. First, the analysis of stage specific matched cohorts provides a better understanding of staged-based outcomes that limit prior retrospective studies. Secondly, their investigation compares a highly selected matched cohort of patients receiving chemoradiation therapy with patients receiving guideline based trimodality therapy (surgery and adjuvant chemoradiation therapy) providing an outstanding source of evidence-based data outside of a randomized prospective trial.

When specifically examining the role of surgery in SCLC, there are a few recent retrospective studies, including ones that have used the NCDB, addressing its role in the multimodality therapy of SCLC (2-5). Historically speaking, there are two randomized studies addressing the role of surgery in SCLC. The first, prior to the use of chemotherapy in 1973, was the Medical Research Council (MRC) trial (6). This study was limited by the fact that it did not include a chemotherapy arm. The second trial in 1994 looking at neoadjuvant chemotherapy followed by attempted resections (7), excluded patients with peripheral lesions which arguably, could have produced better outcomes associated with successful complete resections. It almost goes without mentioning that tremendous strides have been made with chemotherapy drug development, the delivery of radiation therapy, and the performance of surgery for lung cancer, in general, since the era in which these randomized trials were conducted.

In recapitulating some of the authors' significant findings, their survival analysis demonstrated that surgery almost doubled the median overall survival (OS) for stage I (38.6 *vs.* 22.9 months) while also showing a clinically significant longer OS for patients regardless of T stage: T1/T2 N0 (40.1 *vs.* 23.0 months), T3/T4 N0 (33.0 *vs.* 16.8 months). Even among patients with positive nodal disease, they also showed a significantly increased OS: N1 (24.2 *vs.* 18.3 months) and N2 (20.1 *vs.* 14.6 months). To put these surgical results into context, a comparison to international guidelines demonstrates their significance. The European Society of Medical Oncology (ESMO) recommends surgery for T1/2 N0/1 disease with postoperative chemotherapy and consideration given to post radiotherapy (8). Furthermore, they find no role for surgery in N2 and N3 disease and recommended only treatment with chemoradiation therapy. Additionally, the National Comprehensive Cancer Network (NCCN) and American College of Chest Physicians (ACCP) both recommend surgery for only Stage 1 disease (T1/2 N0) (9,10). In consideration of these societal guidelines, Wakeam *et al.* study challenges current thinking regarding nodal disease and opens the door for further conversation about the surgical management of

these patients. These contrasting results further support the possible need for a prospective trial for SCLC patients with nodal disease.

It is surprising to learn that approximately 60% of surgical patients in the staged cohorts had a sublobar resection. Despite the relatively frequent use of sublobar resections, the authors still manage to demonstrate that regardless of clinical stage, patients undergoing lobectomy fare the best. It is not clear why sublobar resections were used so commonly in a disease that is phenotypically aggressive. The rationale for the common use of sublobar resections is most likely varied, but could include that fact that they were employed for diagnostic rather than therapeutic purposes. In light of these findings, one can theorize the survival advantage of surgery may have been greater had lobectomies been performed with greater frequency.

In their subset analysis of chemoradiation therapy versus trimodality therapy with lobectomy and adjuvant chemoradiation therapy, the authors showed that trimodality treatment was associated with a significantly longer OS (48.6 *vs.* 28.7 months). Although this revelation is a remarkable finding in and of itself, it speaks to a more important "message behind the message" which is that using trimodality therapy in treating SCLC requires a coordinated effort of forward thinking clinicians from different subspecialties within a strong multidisciplinary team. The act of including surgical therapy with node positive disease in patients with SCLC is an example of a concerted programmatic effort. At many large institutions, these efforts are implemented via multidisciplinary tumor boards bringing together physicians from oncological, radiological and surgical services. During these tumor board conferences individualized, disease specific treatment plans are discussed, decided upon, and implemented, implying a consensus agreement to these plans.

Although no study is without its shortcomings and understanding the NCDB has its own inherent limitations, the authors should be praised for minimizing these limitations. The use of the NCDB prevents disease free survival analysis and limits the authors understanding of the selection of operative candidates as this data is not provided. The totality of nodal disease burden is not recorded which may have affected surgical selection bias, however, only affecting those patients with positive nodes. In addition, when node positive patients were propensity matched, survival differences associated with the addition of surgical therapy proved not to be statistically significant. These results align with prior studies (2,11) demonstrating nodal status as the driver of poor outcomes. Although, this finding precludes a definitive conclusion regarding the surgical treatment of SCLC patients with nodal disease, these results, nonetheless, add more data to the growing body of evidence suggesting nodal disease is the strongest prognostic factor in patients with SCLC.

Wakeam and colleagues provide us with stout framework and guidelines to support our clinical decision making in treating SCLC patients. Their results highlight the continued need for structured ongoing investigations, including a possible randomized trial, to answer the unanswered questions with respect to SCLC.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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