Editorial Commentary

Surgery for early-stage small cell lung cancer: is it worth it?

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We commend Yang *et al*. on their recent population-based analysis entitled "Long-term Survival After Surgery Compared with Concurrent Chemoradiation for Node-negative Small Cell Lung Cancer" that was recently published in *Annals of Surgery* (1). National Comprehensive Cancer Network (NCCN) guidelines state that in patients who are medically operable, surgical resection and adjuvant chemotherapy (± radiotherapy) remain standard of care for those with early stage, node-negative small cell lung cancer (SCLC) (2). Yet the data supporting such an approach remain limited to antiquated prospective trials that included SCLC patients with node-positive disease (3-5) or small institutional series that contained a heterogeneous mixture of SCLC stages and chemotherapy and radiation treatment approaches (6-8). The paucity of prospective data in the literature is a testimony to the rarity of early stage, node-negative SCLC found at presentation. SCLC accounts for approximately 12% of all lung cancers in the United States, and of those new diagnoses, less than 5% of those patients present with early stage, potentially operable disease (9). As such, planning a sufficiently powered randomized trial comparing standard-of-care chemoradiation (CRT) (10,11) to surgical resection followed by adjuvant therapy is not feasible.

Population-based analyses offer the advantage of large patient numbers, especially with rare disease entities such as early stage SCLC, and although they are retrospective in nature, they provide an excellent resource for patterns-of-care studies. Yang *et al*. have conducted the first analysis comparing surgery with adjuvant chemotherapy (± radiotherapy) *vs*. CRT in cT1-T2N0 SCLC patients utilizing the National Cancer Database (NCDB) (1). With appropriate exclusion of patients with prolonged time from diagnosis to surgery or CRT, the investigators thoroughly performed both a multivariate Cox regression analysis and a 1:1 matched propensity study to compare survival between the two groups. They found a statistically significant improvement in overall survival with surgery. There was a 40% relative decreased risk of death in patients who underwent surgical resection when compared to those who had CRT therapy alone after accounting for certain socioeconomic and disease characteristics (hazard ratio: 0.61, 95% CI: 0.53–0.71; 5-year survival: 29.8% *vs*. 47.5%; P<0.01).

Cautious interpretation of survival outcomes when using population-based data, however, is warranted. The NCDB lacks any information on patient selection, staging studies (positron emission tomography/computed tomography (PET/CT), brain imaging) or salvage treatments given. It is certainly possible that patients who were considered for upfront surgical resection had more favorable demographic characteristics not reported in the NCDB, such as improved performance status, pulmonary function reserve, or social support, all of which can influence outcomes in lung cancer (12,13). Furthermore, mediastinal assessment and clearance with a lung cancer diagnosis is imperative, as it

strongly correlates with survival (14-16). However, it is not reported in the NCDB how the mediastinum was staged in cT1-T2N0 SCLC patients who underwent CRT. As is known with stage I non-small cell lung cancer (NSCLC), patients treated with radiation therapy generally receive less extensive or less invasive lymph nodal staging compared with patients receiving surgical resection, resulting in up to one-third of patients who are treated with radiation therapy for presumed stage I NSCLC having nodal metastasis (17). This bias in nodal staging can certainly impact survival and may be even more pronounced for SCLC, a cancer with higher nodal metastasis rates. Indeed, 20% of the surgical cohort had pathologic upstaging of nodal disease at the time of surgery, further underscoring this difference in surgical versus clinical staging in the CRT group that is unaccounted for by this analysis (1). Also, the NCDB lacks specific information on toxicity data besides the reported 3.7% readmission rate and 90-day mortality rate of 2.1% reported in the manuscript. However, one would expect the toxicities of node-negative patients compared with larger-volume node-positive CRT patients or even surgery patients to be minimized in the setting of advanced radiation delivery, image-guidance and modern target volumes that would limit dose to the heart and esophagus.

Additionally, information on patterns-of-failure and specific chemotherapy regimens is also lacking with NCDB studies. While we would expect excellent rates of local control with surgery, the predominant failure type in patients with limited stage SCLC is more often distant, accounting for 50–60% of failures (18,19). Thus, chemotherapy remains critical in the treatment of SCLC, even when limited to stage I disease (20). Although Yang *et al.* did limit their analysis only to those patients who underwent CRT or adjuvant chemotherapy after surgery, the number of cycles and the types of chemotherapy utilized could not be assessed for the two cohorts using NCDB.

Furthermore, due to the high rates of distant failures in patients with early stage SCLC, more rigorous assessment of the potential benefits of surgery and an evaluation of its risks as well as recovery time and chemotherapy delays need to be clarified and placed in the context of alternative local therapies. In patients with early stage, node-negative NSCLC, stereotactic body radiation therapy (SBRT) has become established as the standard of care treatment approach for patients who are medically inoperable or decline resection (21) and has emerged as a viable alternative to surgery in operable candidates, with comparable outcomes in terms of local control and survival (17,21,22). Furthermore, there have been recent multi-center analyses relaying promising results with the use of SBRT in cT1-T2N0 SCLC patients (20,23,24). In our multi-institutional study of 74 patients with early stage SCLC treated with SBRT, excellent local control was achieved (3-year local control 96.1%), with a median survival of 31 months after receiving chemotherapy (24). Furthermore, a multi-center Japanese retrospective study of 43 patients with early stage SCLC treated with SBRT reported 2-year local control and overall survival rates of 80% and 72%, respectively, despite only 8 of these patients receiving systemic therapy (20). In fact, the use of SBRT for early stage SCLC has increased significantly over the past decade, highlighting the feasibility of this approach (25). Although the study by Yang *et al.* did not compare surgery to SBRT in this rare cohort of patients, it is still an important treatment option to consider, especially in patients who are at such high risk for distant metastasis after local therapy.

Deciding on whether surgery or radiation therapy (as SBRT or as CRT) should be used as definitive local treatment in patients with early stage SCLC remains a matter of controversy, and when considering the rarity of the disease entity, this will most likely never be answered in a randomized, prospective fashion. In the absence of such data, this population-based study by Yang *et al.* provides additional evidence to support the current NCCN recommendations for surgery in early stage SCLC patients. Patients should, however, be well selected, and providers should be aware of the importance of complete systemic (i.e., PET/CT and MRI brain) and nodal (mediastinal assessment) staging prior to surgery, the need for adjuvant platinum-based chemotherapy, and the utility of alternative local therapies, particularly of SBRT for medically inoperable patients.

Acknowledgments

None.

Footnote

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

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