Knowing the Bad: Adverse Event–Informed, High-Risk, Early-Stage Non-Small Cell Lung Cancer Treatment Options

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Despite advances in immunotherapy, surgical techniques, and radiation therapies, lung cancer remains the leading cause of cancer-related mortality, both in the United States and worldwide (1, 2). Overall 5-year survival rates are poor (~22%), because most patients present with advanced stage disease. Surgical lobectomy with mediastinal lymph node dissection (MLND) has been the first-line standard of care treatment for patients with early-stage non–small cell lung cancer (NSCLC) who are considered to be good operative candidates for decades (3). Standard-risk patients are considered to have an operative mortality risk of <1.5% and undergo a lobectomy with limited anticipated perioperative morbidity (4). For those deemed as increased or high risk for lobectomy, alternative therapies include sublobar resection (anatomic segmentectomy or wedge) and stereotactic body radiation therapy (SBRT) (5). However, there is considerable debate regarding the optimal treatment for patients with localized NSCLC who are deemed high risk or medically inoperable for a lobectomy (6).

In this issue of *AnnalsATS*, Wang and colleagues (pp. 2053–2061) compare adverse events (AEs) after limited resection and SBRT for clinical early-stage (I–IIA) NSCLC in an attempt to provide important patient-centered outcome data to help patients and physicians make more informed decisions about cancer care (7). As noted by the authors, there is a lack of well-powered, randomized controlled trials comparing the oncology outcomes of surgery versus SBRT. In addition, meta-analyses and systematic reviews have been limited by small numbers of patients, disparate study design, varying definitions of outcomes, and mixed results, leading to a lack of consensus regarding the best treatment approach for these high-risk patients (7).

Using a prospective, multiinstitutional observational cohort design, patients with primary NSCLC with no clinical lymph node involvement and tumors <5 cm, who were at high risk for lobectomy with longitudinal follow-up, were included (7). Appropriately, patients with prior lung radiation or history of prior cancer within 5 years were excluded. In total, 509 patients were approached for enrollment, and 387 consented. Ultimately, 252 patients had 30- and 90-day follow-up assessments and were included in the study, with 88 (35%) receiving limited resection and 164 (65%) receiving SBRT. Of the 509 patients approached, the authors note that 79% underwent video-assisted thoracoscopic resections and 10% underwent robotic resections, but they do not give a detailed breakdown of the surgical approach for the 88 patients who underwent limited resection and were actually included in the analysis or whether these patients underwent MLND. Not surprisingly, before treatment, there were significant differences between the two groups in terms of age, race, education level, insurance status, comorbidities (stage of chronic obstructive pulmonary disease, hypertension, and cardiovascular disease), cognitive function, functional status, and cancer stage. This would indicate a level of selection bias toward one treatment over the other by either the treatment team or the patients, with arguably healthier patients undergoing surgery. Unadjusted analyses demonstrated no significant differences in the development of at least one AE within 30 days of treatment, with most AEs being classified as mild. Of note, surgical patients were more likely to develop respiratory and infectious AEs, and patients with SBRT were more likely to report fatigue. Similar findings were noted at 90 days posttreatment, but with no difference in infectious AEs and a higher risk of cardiovascular AEs in the surgery group. Similar findings were noted when propensity score methods were used to adjust for differences in the baseline characteristics of the two groups.

The strengths of the study by Wang and colleagues (7) include the prospective, standardized data collection from a geographically diverse set of five institutions across the United States. With a relatively large number of patients included in the analyses, it is powered to detect differences in the most common AEs, and the authors have attempted to control for baseline differences between the two treatment groups with propensity matching. These data highlight and provide useful, real-world information in counseling patients with NSCLC who are considered high risk for lobectomy about the likelihood of AEs with each form of treatment. Although it would seem that the majority of the surgical patients underwent a minimally invasive approach, there is a lack of granularity to confirm this, and they do not mention whether these patients underwent a MLND, which has the added benefit of pathologically staging the hilar and mediastinal lymph nodes. Further details regarding the surgical procedures performed on the included patients would help inform the relatability of the AE data to clinical practice, as minimally invasive approaches are known to have improved short-term outcomes compared with a thoracotomy (8, 9).

Ultimately, the uncertainty of long-term oncologic outcomes directly comparing SBRT and limited resection remains. The study by Wang and colleagues (7) was not designed to answer this question, but, hopefully, the authors will follow these

DOI: 10.1513/AnnalsATS.202209-756ED

patients and provide these data in a future study. Previous reports note 5-year overall survival of 40–55% and disease-free survival of 25% with SBRT (4). A recent comparative effectiveness study using data from the National Cancer Database from 2004 to 2016 of nearly 26,000 stage I patients with NSCLC noted that surgery (both lobectomy and sublobar resection) was associated with improved survival relative to SBRT in otherwise healthy patients whose Charlson-Deyo Comorbidity Index score was 0 (10).

From a surgical perspective, the question of oncologic equivalence of sublobar resection compared with lobectomy has remained a controversial topic. Benefits of a sublobar resection over SBRT include the ability to perform an MLND and provide pathologic staging of hilar and mediastinal lymph nodes to confirm localized disease. Recently, two trials have provided high-level evidence to compare the oncologic outcomes of lobectomy and sublobar resection in the era of minimally invasive procedures. The Japan Clinical Oncology Group and the West Japan Oncology Group (JCOG0802/WJOG4607L) study demonstrated similar 5-year overall survival for segmentectomy ($n = 552$) and lobectomy ($n = 554$) (94.3% vs. 91.1%, respectively) in patients with <2 cm peripheral lung NSCLC (11). Twenty-two patients were converted intraoperatively to a lobectomy; 3% of patients had hilar nodal disease and 3% had ipsilateral mediastinal nodal disease. Similar rates of grade 2 or greater postoperative complications were seen between the two groups. Of note, in this study, the risk of local recurrence was 10.5% for segmentectomy and 5.4% for lobectomy ($P = 0.0018$). In addition, the Cancer and Leukemia Group B 140503 study is a large, multicenter, randomized trial comparing sublobar resection to lobectomy (12). Long-term oncologic findings from this study were recently reported as noninferior with sublobar resection for overall and disease-free survival for clinical T1aN0 NSCLC at the World Conference on Lung Cancer 2022 in early August, but further details are forthcoming in a peer-reviewed publication. These studies would seem to indicate that sublobar resection with MLND offers similar long-term survival outcomes to lobectomy in patients with NSCLC with tumors <2 cm and negative lymph nodes in patients who are healthy enough to have surgery.

Clearly, the debate for optimal treatment for high-risk patients undergoing lobectomy will continue. The involvement of a multidisciplinary team in deciding the most appropriate, individualized care for these patients is paramount. Local resources, provider expertise, and patient preference regarding possible treatments must all be heavily weighed when deciding on a treatment plan. This study (7) adds important, generalizable, real-world data to the armamentarium for helping patients decide which treatment may be best for them. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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