Editorial

Comparing apples to oranges: short-term mortality after surgery versus stereotactic body radiotherapy for early-stage non-small cell lung cancer

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

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

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

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Lung cancer is the leading cause of cancer-related death in the United States (US) with 224,390 new cases and 158,080 deaths estimated in 2016 (1). For patients with early stage (stage IA–IIA) non-small cell lung cancer (NSCLC), surgical resection provides the best chance for cure (2). In the past decade, stereotactic body radiotherapy (SBRT) has emerged as an alternate to surgical therapy for high medical risk patients with localized disease. Multiple analyses, including meta-analyses and Markov decision models, have suggested oncologic outcomes comparable to resection in medically inoperable patient populations with regard to locoregional control, disease-free survival, and overall survival (3-9). However, the data regarding short-term outcomes, including morbidity and mortality due to treatment, is limited.

To address this gap in the literature, Stokes *et al.* published their analysis of 30- and 90-day mortality for patients with stage T1-2a N0 M0 NSCLC who had undergone either surgical resection or SBRT (10). Data were obtained from the National Cancer Database from 2004 to 2013. The authors used Cox proportional hazards models to compare the hazard of treatment-related mortality after adjusting for available confounders. They stratified both the unadjusted and adjusted analyses by 5-year age ranges to determine if the effect of treatment on mortality was different for different age categories. Lastly, they selected a propensity-score-matched cohort in whom to confirm their initial findings. The authors found a slight increase in mortality after surgery as compared to SBRT. Age was a significant treatment modifier; patients aged 61 years or older had a significantly increased risk of 30-day mortality and patients aged 71 years or older had a significantly increased risk of 90-day mortality. The authors conclude that this information should be used in treatment discussions with patients.

This study's primary strength is that it asks and attempts to answer an important question typically excluded from other comparisons of SBRT and surgery. Most long-term survival analyses exclude patients who die as a result of treatment, or include a time variable to account for the changing risk of death over time (a violation of the assumption of proportional hazards). Thus, the information available to date examining perioperative or post-treatment mortality has been limited. This important contribution will allow patients and providers to weight the benefits of long term survival together with the risks of short term mortality.

The study also provides some additional important findings. First, the authors found that surgery was more likely to be used for T2 tumors than for T1 tumors in the patients included in the dataset. This is finding is concerning because surgical treatment is likely to afford the best chance for cure in patients with T1 tumors. Second, other than in patients undergoing pneumonectomy, 30- and 90-day mortality rates were quite low for both SBRT and surgical resection. Given this similarity in perioperative risk, the absolute difference between cohorts is so small that the number needed to treat to avoid one excess death at 90 days is 189 (for lobectomy versus SBRT) or 295 (for sublobar resection versus SBRT). Lastly, the authors' primary conclusion is that there is a significant interaction between age and treatment, such that older adults seem to benefit more from SBRT in the short run. While this may end up being an important point to consider during shared decision making with older adults, physicians should be aware that these findings could lead to age discrimination. This is especially concerning because the authors were unable to account for age-related variables that may be influencing these results (such as pulmonary function tests, frailty scores, and performance status). Many studies have cautioned against denying patients surgery based on their chronologic age alone (11).

While the findings reported herein help address an important gap in the literature, the study does have specific limitations that should be mentioned. First, the report lacks a completely transparent description of the methodology used, especially with regard to the analysis of the propensity-score-matched cohort and the definition of variables (e.g., facility volume). Additionally, there are other methodologic inconsistencies. For example, there are three different ways of dealing with the age variable: continuous, 5-year groupings, and quartiles. Second, the cohorts were defined based on clinical stage and as a result some pathologic confirmation for SBRT patients is lacking. While this is more relevant for a long-term survival analysis, it is also important to consider when interpreting the near-term findings. Third, as the authors admit, they are unable to account for some important confounders such as pulmonary function, specific medical comorbidities, and performance status. Because these factors are often correlated with age, the effect modification the authors report may be due to one of these potential hidden confounders rather than to the treatment strategy itself. Fourth, the patient cohort included a wide range of surgical patients (e.g., pneumonectomy patients) and these higher order resections, which are known to carry increased risk, may have biased the results against surgery. Fifth, as a methodologic weakness, the authors did not report any sensitivity analyses that might have been performed for the propensity score matched analysis. Because there are many decisions that must be made for this type of analysis, the robustness of the results should be verified through sensitivity testing. Lastly, the findings for 90-day mortality (which showed less of a survival benefit to SBRT than that seen at 30-days) may reflect a medically comorbid cohort that would not have been eligible for surgery. It appears the authors did not exclude patients who likely were not surgical candidates (e.g., comorbidity score of 2+ or 1+ and age >85, etc.).

The study does have potentially important implications for future care paradigms. First, better data from randomized trials are needed to assess important end points such as short- and long-term survival, treatment morbidity, quality of life, and utility/costs. Participation in ongoing trials is important for the thoracic oncology community and should be encouraged, as the authors advocate. Second, future observational studies should carefully choose their cohorts to ensure similar patients are being considered. This study included patients undergoing higher order resection (patients with tumors that may not have been ideal targets for SBRT). Lastly, future studies should consider the quality of the operation itself. While these patients were all treated at a Commission-on-Cancer (CoC) accredited center, we have no way of determining if their surgeon was for example, a general surgeon that occasionally performed lung resection or a board-certified thoracic surgeon at a high-volume center that participates in the Society for Thoracic Surgeons database. Many studies indicate that there is wide variation in care, even among CoC-accredited centers (12). These variations need to be considered if we are to gain an accurate understanding of the comparative effectiveness of SBRT versus best surgical therapy.

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Footnote

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

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