Editorial

Stereotactic body radiotherapy for operable, early stage non-small cell lung cancer—let's all take a deep breath

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In spite of a federally mandated emphasis on smoking cessation and primary prevention, lung cancer remains by far the most common cause of cancer death and carries a 5-year survival rate (~18%) that is far lower than that of other leading cancers (1). Indeed, even in the modern era, lung cancer accounts for more deaths than breast, prostate, and colon cancer combined, and 80% to 90% of patients who develop lung cancer will ultimately die of their disease (2). With the recent development of lung cancer screening programs in the United States and around the world, there is renewed hope that early detection of non-small cell lung cancer (NSCLC) in at-risk populations will result in prompt interventions and higher rates of cure for those with early stage disease. Consequently, the developing focus on both cost- and treatment-effective care, especially in those patients with early stage lung cancer, is of utmost importance and has prompted a recent upsurge in research comparing novel therapies against more standard pathways of care.

In this issue of the Journal, Stokes and colleagues (3) present their retrospective analysis of the National Cancer Database (NCDB) comprising 84,839 patients who underwent either surgery (n=76,623) or stereotactic body radiotherapy (SBRT, n=8,216) for the treatment of early stage (cT1-T2a, N0M0) NSCLC. Using all-cause mortality as their primary endpoint, the authors report slightly higher 30- and 90-day mortality rates among those who underwent surgery compared to those who received SBRT in unadjusted, propensity matched and multivariate analyses. Further age-related subgroup analyses reveal that mortality rates were higher after surgery compared to SBRT for each age subgroup with the exception of 30-day rates in patients less than 55 years of age and 90-day rates among those younger than age 65. Differences in early mortality between surgery and SBRT were shown to increase with extent of resection, particularly in patients greater than 70 years of age. The authors conclude that these differences in early mortality will better inform shared decision-making discussions in patients with early-stage NSCLC who are eligible for both surgery and SBRT.

Although the differences in short-term mortality reported by Stokes *et al.* are compelling, one must recognize that they are also expected. Any invasive procedure inherently carries more up-front risk than the non-invasive alternative. The fact that the primary outcome of all-cause mortality was only assessed to 30- and 90-day post-procedure makes the significance of these small, retrospectively observed mortality differences difficult to interpret. Rather than focusing on the short-term mortality differences between SBRT and surgery, a more important take away from this study is that the reported short-term mortality associated with surgery is remarkably low, with an absolute rate of mortality of 2% at 30-day and 2.1% at 90-day for patients undergoing lobectomy. This is similar to a recent 2016 review of the Society of Thoracic Surgery General Thoracic Database (STS-GTD) which reported

an overall mortality rate of only 1.4% after lobectomy (4). What is striking about these findings is that while the STS-GTD primarily represents board certified thoracic surgeons, the NCDB captures an unselected cohort of all surgeons performing pulmonary resections and is therefore is much more generalizable and a good representation of the current state of thoracic surgical outcomes.

Within their discussion, Stokes and colleagues draw attention to the fact that patients who underwent sublobar resection "tended to experience greater mortality than those undergoing SBRT," except in those patients comprising the youngest age groups (<65 years old) (3). The finding that even sublobar resection carried greater mortality than SBRT should not come as a surprise, as traditionally, sublobar resection has been reserved for patients with poor pulmonary reserve or who are otherwise thought to be poor candidates for anatomic resection due to various comorbidities (pulmonary hypertension, poor functional status, etc.). Lobectomy has long been the gold standard for patients with even early stage lung cancer (5) and only in recent years (after this study period) has there been a paradigm shift toward elective sublobar resection for early stage lung cancers, although this too remains controversial (6). Unfortunately, because the NCDB does not capture smoking status, baseline pulmonary function, cardiovascular fitness or performance status, these comorbidities, which are frequently the deciding factor for surgery, could not be included in the analysis and limit the strength of the study.

Within the Stokes study, a significant interaction between older age and mortality was also reported, specifically, that the mortality rates with surgery compared to SBRT increased among patients in age groups >71-year-old (3). Again, this is not surprising, as it is well known that mortality increases with both age and surgical complexity (7). Of note, lobectomies account for the majority of resections in the study, however the given data does not differentiate between lobectomies performed via thoracotomy and those using minimally invasive techniques such as video assisted thoracic surgery (VATS), which was rapidly gaining in popularity during the study period. This may have bearing on the higher 30- and 90-day mortality rates, as numerous studies have cited decreased postoperative complication rates including arrhythmias and pulmonary complications such as pneumonia and prolonged air leaks with VATS lobectomy compared to open lobectomy (8-13). Thus, if one were to look at modern data, now that 50% of lobectomies are performed via a VATS approach and are used increasingly in the elderly due to the association, this mortality rate may be lower, like reported in the STS General Thoracic Database, and no longer show different early outcomes compared to SBRT (14,15).

Within the discussion the authors posit that patients place a greater emphasis on short- than long-term outcomes. While it is true that many patients rely on post-operative morbidity and mortality to guide treatment decisions, most also remain interested in long-term survival, which cannot be overlooked during shared decision making conversations. Rosen and colleagues recently published a retrospective review that looked at healthy patients with stage I lung cancer who underwent either lobectomy or SBRT (16). They found a marked, long-term survival difference (30%) in favor of surgery at 5-year follow-up in propensity-matched cohorts (59% *vs.* 29%, P<0.001) (16). Although the findings of improved long-term survival in the Rosen study are not necessarily surprising given the definitive nature of a R-0 surgical resection, they do reinforce the fact that regardless of a mild increase in peri-procedural risk, surgery still offers a major long-term survival benefit. A similar survival benefit at 5 years was seen in a recently published study comparing SBRT and surgery in Veterans with early stage lung cancer (17). The take away from both of these studies is that surgery is still the gold standard when it comes to the management of early stage lung cancer in medically operable patients.

Although the findings of Stokes and colleagues are intriguing, it is imperative to frame the discussion regarding the choice between surgery and SBRT in the appropriate clinical context. Unfortunately, the oft-cited prospective, randomized trial published in 2015 by Chang and colleagues in *Lancet Oncology* that forms much of the foundation for the use of SBRT in medically operable patients is significantly flawed (18). First, the trial consisted of a pooled analysis of two failed trials (STARS and ROSEL) in which enrollment stopped due to the inability to accrue patients. Not only did the study suffer from inadequate numbers (n=58), it was also tarnished by incorrect data analysis in which the authors reported statistical significance of improved overall 3-year survival in patients undergoing SBRT despite a large wide 95% confidence interval of 0.017–1.190 that negated the conclusion (18). Despite this, advocates of SBRT continue to cite Chang and colleagues' pooled analysis and use it as the basis to claim "clinical equipoise" between SBRT and surgical resection for early stage lung cancer, which simply does not exist.

Stokes and colleagues are correct in their assertion

that an understanding of mortality data is important to informing shared decision-making discussions regarding treatment of early stage lung cancer. However, the implication that increased early mortality should sway patients and providers away from surgery and toward SBRT for early stage NSCLC is incorrect and is a disservice to both patients and naïve providers. The initial trade-off between a 1.5% 90-day mortality benefit of SBRT versus a 30% 5-year survival benefit of surgery will likely result in surgery continued to be favored by patients who are fully informed in shared decision-making. In addition to long-term survival benefit, surgical resection also offers the ability to confirm histology, provide accurate nodal staging and margin assessment, access centrally located tumors or those with airway involvement, and provides easier interpretation of post-procedure surveillance imaging with less risk of locoregional recurrence (16,19,20). As a result, for medically operable patients, surgery continues to offer a more definitive and effective treatment option.

Based on all of the available evidence and in accordance with the most recent National Comprehensive Cancer Network (NCCN) and American Society of Radiation Oncology (ASTRO) guidelines, SBRT should continue to be viewed as second line-therapy for the treatment of NSCLC, and should be reserved for cases of medically inoperable disease, in prohibitively high risk patient populations, and in patients who refuse surgery after thorough shared decision-making discussions (20,21). When taking the full scope of cancer care into account, both short- and long-term outcomes matter. Although there is undeniably a slightly higher procedural risk associated with surgery, both the up-front and long-term benefits of surgery clearly outweigh the short-term risks in medically operable patients with lung cancer.

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Footnote

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

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