Editorial

Stage I lung cancer—to operate or to radiate? that is the question

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As innovations and new technologies enter the market, they are naturally compared to existing ones. In some industries, the benefit or popularity of a newly developed item rapidly replaces the existing one. It is hard to imagine, for example, a randomized trial comparing the usability of a smart phone to a regular cell phone or a comfort and speed of a new car model compared to an older one. Changes in these customer-based industries occur rather rapidly and assertively as new technologies replace older ones.

In healthcare, innovations and subsequent change in medical practice occur at a much slower pace, mainly because customer-based priorities such as design, cost or convenience are not the only factors driving the change. Rather improvements in measurable outcomes in procedural morbidity, disease recurrence, survival, or quality of life eventually modify medical practice guidelines. Only after accumulating enough evidence from well-designed studies comparing the "new" and the "standard" that demonstrate either the superiority or the equipoise of the "new" can a status quo be altered. However, when an unequivocal evidence for superiority or equipoise of a given therapy is lacking, much is left to individual's ability to interpret and maneuver through the available published data. This is the current state of debate between the standard of care for early stage I lung cancer represented by surgical lobectomy with mediastinal lymph node dissection, and the new technique of stereotactic body radiation therapy (SBRT).

Removal of the pulmonary lobe, in which the cancer resides, with intra-lobar and mediastinal lymph nodes has been considered the standard of care for stage I lung cancer for decades, and much literature has been accumulated about surgical outcomes as well as survival outcomes of this treatment paradigm (1-5). However, surgical therapy is applicable only in a subset of patients physiologically fit to undergo pulmonary resection, and therefore many patients who have not qualified for lung cancer surgery have been referred to radiation oncologists for primary radiation of the tumor as a second-best alternative for local disease control. Following the advent of SBRT, this radiation technique found its applicability in the treatment of inoperable stage I lung cancer patients (6). Based on the encouraging short-term results of SBRT for local tumor control, momentum was subsequently gained to challenge the "standard" treatment, surgical lobectomy, in patients fit enough to undergo pulmonary resection. In fact, the motivation to prove at least equipoise between surgical lobectomy and SBRT, led to the design of two phase III randomized controlled trials that directly compared the efficacy of SBRT with lobectomy in patients with early stage non-small cell lung cancer (ROSEL trial and STARS trial). Unfortunately, the attempt to accrue sufficient numbers of patients failed in both trials (6,7). And this failure was not subtle, as STARS accrued only 36 (3%) out of a planned accrual of 1,030 patients over a 5-year period, and ROSEL randomized only 22 (2%) patients out of intended 960 (7). Neither one of these trials was anywhere near the accrual to even attempt an interim analysis. However, authors of both studies decided to combine the data of those 58 patients, and publish the results under the label of "pooled analysis of two randomized trials" (7). And since on the surface, the results looked promising in favor of SBRT, the results were widely hailed in the media as new "equivalent" therapy to surgery for early stage lung cancer (8).

This has created significant disturbance in the thoracic surgical community, as well as amongst radiation oncologists, and has resulted in a number of editorials and

reviews of this study (9-13). Depending on the medical specialty, these reports either rejected (9,10) or upheld (11-13) the authors' interpretation of this otherwise imperfect study. Though several criticisms of this study have been stated in the literature, there are a few findings, which received less attention. They include the closer focus on the causes of mortality in the surgical arm of STARS trial, and the loco-regional disease control in both surgical and SBRT study arms. The primary study outcome was overall survival (OS) at 3 years based on an intention to treat analysis. Estimated OS in SBRT group was 95% compared to 79% in the surgery group (P=0.037). It should be noted that the mortality rate in the surgical arm was excessively high as compared to the current standards for surgical resection of stage I lung cancer, and it is also significantly different between STARS and ROSEL trials, thus skewing the results of the pooled analysis towards STARS outcomes alone. In STARS, 5 out 16 (31%) surgical patients died within 18 months of surgery, as compared to 1 patient in the ROSEL trial who died more than 3 years after surgery. The mortality was due to disease progression in two patients, one patient died from a second lung cancer which rapidly progressed, two died from other comorbid conditions, and there was one death in the perioperative period (4%), which is four times higher than expected perioperative mortality in high volume centers. Besides the sole perioperative death, it is impossible to attribute any other mortality in the surgical arm to surgical therapy. Since limited enrollment (58 patients) precludes the benefit of randomization in equalizing comorbidity, disease states, and unforeseen outcomes among test groups, the endpoint of overall survival is likely not the best primary outcome measure for the comparison of these two inherently local and loco-regional cancer therapies. In such a small cohort, loco-regional disease recurrence may be a more accurate therapeutic endpoint, although SBRT treats only tumor within the lobe, and surgical lobectomy also addresses incidental intra-lobar and mediastinal nodal disease.

Another interesting fact about the STARS trial is that 54 patients who were offered enrollment subsequently elected to have surgery, and 9 patients elected SBRT rather than randomization. Additional outcome analysis of these 63 patients would have shed the light on a potential selection bias of participating patients in the trial. Lastly, loco-regional recurrence was lower in the surgical arm with only 1 patient developing isolated regional recurrence compared to 5 patients in SBRT group (1 local and 4 regional recurrences). Two patients in each arm developed distant recurrence. These results suggest that loco-regional disease control was in fact better in the surgical arm, yet the intention-to-treat overall survival analysis presents the results differently (7).

Since the randomized trials did not answer the question whether SBRT is equivalent to or better than surgical lobectomy in the treatment of stage I lung cancer, the next logical step was to look into large databases to evaluate the results of both therapies. While randomization in such a setting is impossible and selection bias is invariably present, propensity matching statistical technique can be utilized to simulate randomization retrospectively, to lessen bias. Recently, the National Cancer Database (NCDB) has become the most popular and most studied database to answer important questions in thoracic surgery that would otherwise require large randomized studies. In the July 2016 issue of the *Journal of Thoracic and Cardiovascular Surgery*, Rosen and the team from Yale University compared overall survival of "healthy" patients who underwent either lobectomy or SBRT for stage I non-small cell lung cancer (14). The NCDB query identified 13,562 patients who underwent lobectomy and were coded in the database as having Charlson-Deyo score 0, implying that these patients were free from significant comorbidities. Additionally, 1,781 patients were identified with clinical stage I NSCLC and Charleson-Deyo scores of 0 who underwent SBRT. Through a series of analyses culminating in the propensity matching of 1,781 patients, surgical lobectomy was associated with significantly better 5-year overall survival than treatment with SBRT (59% *vs.* 29%, P<0.001). The authors concluded that surgical lobectomy is superior to SBRT, but at the same time proposed yet another prospective clinical trial with sufficient accrual to compare the effectiveness of these treatments (14).

Although the combined analysis of STARS and ROSEL trials had its flaws, the study by Rosen *et al*. is imperfect in many ways as well. First, survival in both groups appears much lower than previously published for stage I lung cancer. (I) Likewise, 90-day mortality in the surgical cohort of 5% is higher compared to other studies (II) and databases (15) although other reports demonstrated similar 90-day mortality albeit in a larger thoracic patient population, rather than stage I patients alone (16).

Unfortunately, the NCDB does not contain detailed information on clinical staging, and it is unclear whether staging was performed utilizing computed tomography alone or with the addition of positron emission tomography or with invasive methods. The authors acknowledge that

only 6% of SBRT patients had lymph nodes evaluated (14). How many nodes or which mediastinal stations were evaluated is also unknown. Likewise, it is unknown what the pulmonary function was in either group or what led providers to recommend one type of therapy over another. These limitations cannot be overcome by propensity matching and it is fair to assume that even though the authors made every effort to analyze similar patient populations there are still differences that cannot be accounted for. It would be interesting to know, how many patients with clinical stage I were upstaged after surgical resection or what was the therapeutic efficacy of both therapies in tumors ≤2 cm in size. Approximately 30% of patients in the surgical cohort and 23% in the SBRT group had cT2 tumors, yet chemotherapy variable was not utilized in the survival analyses model. On the other hand, it is unknown how many patients had tumors >4 cm in size, and the survival benefit of chemotherapy (~5%) would have likely not altered overall results. An important observation from the Kaplan Meier graphs is the consistent trend in crossover in survival between 10–12 months post treatment arguing for the initial safety of SBRT. Overall, it is difficult to draw definitive conclusions from this study except that the overall survival for stage I lung cancer in NCDB database appears to be worse for both lobectomy and SBRT than wound be expected based on the results of other smaller or single institution studies, underscoring the importance of patient selection, skill and technique in administering either therapy.

Despite many discussions and opinions about the equipoise of surgical lobectomy and SBRT for stage I lung cancer, the conclusive answer to this question is lacking and cannot be definitively extrapolated from the studies that have been performed so far. The results from the pooled analysis of randomized trials (7) and other single institution SBRT series (6) conflict with the results from the large NCDB propensity matching analysis (14). Is it better to believe the outcomes of pooled randomized trials that present data of only 3% of the expected enrollment thus minimizing the beneficial effects of randomization, or is it better to believe the outcomes of 1,781 retrospectively matched patients without any details about clinical staging or pulmonary function and hence the bias in patient selection?

What we have learned from these and previous studies is that a number of patients who undergo successful lobectomy for stage I lung cancer will be cured with this therapy. Likewise, there is a subgroup of patients for whom SBRT is also curative, and some patients will recur regardless of the treatment approach. Unfortunately, none of the studies have yet identified patient subgroups in which the success of one type of treatment or another would be validated. Considering the failure of randomized trials to accrue patients, further suggestions to organize yet another much needed randomized trial, is more of a utopia than reality, especially in a healthcare system, which incentivizes providers based on the volume and productivity, rather than challenging decision making or patient enrollment on clinical trials.

So, should we operate or should we radiate? For now, decisions regarding the type of therapeutic approach for stage I lung cancer should be discussed prospectively in a mutli-disciplinary setting with shared decision making that highlights both the positive and negative aspects of both treatment options. The knowledge of individual and institutional treatment outcomes for lobectomy as well as for SBRT should be known and taken into account when making an informed decision regarding treatment recommendations and when counseling patients.

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Footnote

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References

1. Stephens N, Rice D, Correa A, et al. Thoracoscopic lobectomy is associated with improved short-term and equivalent oncological outcomes compared with open lobectomy for clinical Stage I non-small-cell lung cancer: a propensity-matched analysis of 963 cases. Eur J Cardiothorac Surg 2014;46:607-13.
2. Allen MS, Darling GE, Pechet TT, et al. Morbidity and

mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg 2006;81:1013-9; discussion 1019-20.
3. Chang MY, Mentzer SJ, Colson YL, et al. Factors predicting poor survival after resection of stage IA non-small cell lung cancer. J Thorac Cardiovasc Surg 2007;134:850-6.
4. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
5. El-Sherif A, Gooding WE, Santos R, et al. Outcomes of sublobar resection versus lobectomy for stage I non-small cell lung cancer: a 13-year analysis. Ann Thorac Surg 2006;82:408-15; discussion 415-6.
6. Ricardi U, Badellino S, Filippi AR. Stereotactic body radiotherapy for early stage lung cancer: History and updated role. Lung Cancer 2015;90:388-96.
7. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol 2015;16:630-7.
8. Rice D, Sepesi B, Heymach J, et al. SABR vs surgery for NSCLC in the media. Lancet Oncol 2015;16:e422.
9. Hamaji M, Groth SS, Sugarbaker DJ, et al. Surgery versus SABR for resectable non-small-cell lung cancer. Lancet Oncol 2015;16:e372.
10. Opitz I, Rocco G, Brunelli A, et al. Surgery versus SABR for resectable non-small-cell lung cancer. Lancet Oncol 2015;16:e372-3.
11. Treasure T, Rintoul RC, Macbeth F. SABR in early operable lung cancer: time for evidence. Lancet Oncol 2015;16:597-8.
12. Moghanaki D, Chang JY. Is surgery still the optimal treatment for stage I non-small cell lung cancer? Transl Lung Cancer Res 2016;5:183-9.
13. Simone CB 2nd, Dorsey JF. Additional data in the debate on stage I non-small cell lung cancer: surgery versus stereotactic ablative radiotherapy. Ann Transl Med 2015;3:172.
14. Rosen JE, Salazar MC, Wang Z, et al. Lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer. J Thorac Cardiovasc Surg 2016;152:44-54.e9.
15. Kozower BD, Sheng S, O'Brien SM, et al. STS database risk models: predictors of mortality and major morbidity for lung cancer resection. Ann Thorac Surg 2010;90:875-81; discussion 881-3.
16. Hu Y, McMurry TL, Wells KM, et al. Postoperative mortality is an inadequate quality indicator for lung cancer resection. Ann Thorac Surg 2014;97:973-9; discussion 978-9.

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