Lobectomy: no port at all?

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Over decades of development, surgical procedures in stage I non-small cell lung cancer (NSCLC) have been advanced from open thoracotomy to video-assisted minimally invasive thoracoscopic surgery (VATS). Lobectomy (with preference of VATS technique) remains the standard of care for stage I NSCLC (1). The unstopping advances in surgical devices and techniques have contributed to the VATS transition from the conventional multiportal approach to uniportal approach, which has demonstrated advantages in safety and preservation of patient's quality of life over the former (2). Curiously, is that possible to perform lobectomy with no port at all, or to rephrase the question, is a noninvasive procedure reasonable and available for definitive treatment of this malignancy with outcomes same to or even better than surgery?

Radiotherapy, as a noninvasive procedure, has been used in treatment of lung cancer for almost a century. In its early days, it was once commented "worse than useless" due to poor efficacy but severe adverse effects (3). Thanks to the advancement in radiotherapy equipment, imaging and treatment planning system, radiotherapy has been leaped from the primitive dark time into the modern and bright era with characteristics of precision, accuracy and individualization. Among numerous emerging radiotherapy techniques, stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) has attracted extensive attentions from the professionals and the public due to excellent therapeutic outcomes in certain localized solid tumors, especially lung cancer. By focusing high-energy radiation beams (X-ray mainly) to ablate tumors, SBRT can be considered as a procedure of tumor resection without any port. The noninvasiveness renders this treatment highly safe even in fragile and elderly patients. As a direct consequence, the introduction of SBRT has dramatically shifted the management strategy for elderly patients with stage I NSCLC with a 16% absolute increase in definitive treatment, a decline in the proportion of untreated elderly patients, and an improvement in OS (4).

The safety and efficacy of SBRT for stage I NSCLC have been investigated in various scenarios, including elderly patients, inoperable patients, patients with borderline comorbidities as well as operable patients. With sufficient supports from high-level evidences, the role of SBRT in elderly and inoperable patients is solid and steadfast. The NCCN guideline on NSCLC has recommended SBRT as an alternative treatment for those patients since the version V.2.2010 (5). Attracted by the excellent local control and acceptable overall survival in inoperable patients, oncologists, especially we radiation oncologists cannot help wondering how SBRT performs in otherwise healthy patients with operable early-stage NSCLC. Many retrospective studies with propensity matched analysis and meta analysis between SBRT and surgery showed encouraging results that SBRT might have comparable local control and overall survival to surgery (either lobectomy or sublobar resection), but some studies just reported opposite results (6). It is not surprising that the debate of SBRT and surgery in operable patients remains one of hot topics

in multidisciplinary thoracic oncology. With the intent to solve the predicament, multiple randomized clinical trials, including ROSEL, STARS, JCOG 0403 and RTOG 0618 were funded. Due to poor accrual, the ROSEL and STARS were early terminated. The pooled analysis showed estimated overall survival at 3 years was 95% in the SBRT group compared with 79% in the surgery group, and recurrence-free survival at 3 years 86% *vs.* 80%, which did not quiet down the debate instead add more fuels. Certainly, this analysis suffered from small patient sample size and short follow-up (7), and received extensive critiques from thoracic surgical colleagues. Despite that, the endeavor in exploring answers is not abating with ongoing prospective studies, including SABRTooTH, RTOG3502, VALOR and STABLE-MATES (8).

In this context, Rosen *et al.* conducted a retrospective study based on the National Cancer Database to compare the efficacy of lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer (9). The major strength of this study is the large patient sample size in both lobectomy and SBRT cohorts. Unlike a meta-analysis, database-based study could have more controls on research objects by imposing strict criteria for query. In the SBRT cohort, "healthy" patients were defined by "a Charlson-Deyo comorbidity index of zero". Using time-stratified Cox proportional hazards models and propensity-matched analysis (PMA), lobectomy appeared superior to SBRT (5-year survival 59% *vs.* 29%, 58% *vs.* 40%, respectively), opposite to the ROSEL/STARS. However, numerically, the 5-year survival in this study is far from satisfactory for both surgery and SBRT in comparison to over 70% in surgery and 50% in SBRT previously reported. The 11% gap in survival between selected SBRT patients for PMA (40%) and the whole "healthy" SBRT cohort (29%) is astonishing, implying that the so called "healthy" SBRT patients may not be as healthy as operable patients. In addition, 16% of patients in surgery cohort received systemic therapy but only 2% in SBRT cohort, which could generate significant impact on survival considering that both surgery and SBRT have been reported to have the similar pattern of failure, i.e. distant metastasis (10). There is no doubt that overall survival is the ultimate study end-point for efficacy evaluation of any treatment approach, including SBRT and lobectomy in stage I NSCLC. Nonetheless, the local control and pattern of failure are important indexes for comparison. Regretfully, this study did not reported results related to both indexes.

Two limitations are not addressed in this study. Both are related to heterogeneity. Firstly, the impact of technical heterogeneity in SBRT protocol should not be underestimated. During the study period of 2008–2012, as an emerging technique with higher requirement than conventional radiotherapy, SBRT was in its fast growing phase and more radiation oncologists initiated their SBRT programs for lung cancer patients. According to a survey, cumulative adoption of SBRT for lung cancer had approximately 5 times of increment from less than 10% in 2004 to higher than 50% in 2010 with various dose fractionation (11). Despite that a stringent definition of SBRT were used based on coding and biologically effective dose (BED), the quality assurance may vary among institutions considering that multiple international authoritative organizations and societies started to publish recommendations to guide and standardize the clinical practice of SBRT from the year of 2009 (12-15). Secondly, heterogeneity in patient selection for both surgery and SBRT may have profound impact on the comparison results. Besides the potential heterogeneity in comorbidity status, the other factor that is worthwhile to be noted but tends to be neglected is the discrepancy in early-stage NSCLC between surgery and SBRT. To be specific, adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) with GGO-predominant lesions (formerly bronchioloalveolar adenocarcinoma, now Tis, T1mi, T1a and part of T1b according to the 8th TNM classification of lung cancer (16) are excluded from SBRT trials mainly due to difficulty in real-time image guidance during treatment delivery and the risk for underdosing the target volume due to a loss of electronic disequilibrium, which could be more than 20% less than the calculated dose (17,18). However, both AIS and MIA are included in the surgery cohort and the proportion is not minimal but consistently growing due to the adoption of low-dose CT screening in high-risk population. Both diseases have an excellent 5-year survival of approximately 100% (19). Therefore, the imbalance in disease composition of early-stage lung cancer apparently favors the results in surgery cohort and could partly explain the better OS in cT1 diseases in this study.

Due to observation of inferiority of SBRT in local control of larger tumors (T2) (20,21) and the predominant pattern of failure being distant metastases in approximately 20% of cases (22), systemic therapy has been hypothesized with potential survival benefit in such patients (23). Multivariable analysis has been conducted with intention to build models to predict patients who may benefit from

adjuvant chemotherapy after SBRT. Among variables investigated, higher pretreatment FDG-PET maximum standardized uptake value, large tumor size (T2), and contact with mediastinal pleura in imaging are of prognostic value for patients with highest risk for distant failure (24,25), justifying the necessity of providing systemic adjuvant therapy (chemotherapy or targeted therapy) to these patients. In Rosen *et al.* study, only 2% of SBRT patients received chemotherapy, much less than 16% in surgery cohort, suggesting that there may be some patients in need of chemotherapy but not receiving in practice due to underestimating the disease severity.

In the treatment of early-stage lung cancer, lobectomy and SBRT are not necessarily a "zero-sum" game. Recently, a phase II clinical trial has been funded to investigate the combination of SBRT and surgery for early-stage NSCLC (MISSILE-NSCLC) with primary outcome measurement of percentage of patients who exhibit a lack of viable tumor after surgical resection (26). The interim safety results reported that the rate of acute grade 3–4 toxicity was 10% and no post-operative mortality occurred at 90 days. More commonly, lobectomy is used as a salvage treatment of local recurrence after SBRT, and vice versa (27-29).

"Loud is its sound, but never word it said", a quote from The Tao Te Ching, one of ancient Chinese philosophies, somewhat reflects the evolution of therapeutic procedures in stage I NSCLC from massively invasive to less invasive to possible noninvasive. In the era of precision medicine, technological advances and clinical research over the past few decades have given radiation oncologists the capability to personalize treatments for accurate delivery of radiation dose based on genomic information, clinical parameters and anatomical information to achieve eradication of gross and microscopic tumors with preservation of health-related quality of life (30,31). And it is anticipated that the efficacy of SBRT will be continuously improved and promising.

Again, is it time for SBRT to overtake surgery as the treatment of choice for stage I NSCLC (32)? The answer is yes and no, dependent on the individual patient. What we are trying to do is to work closely as a part of a multidisciplinary team to serve our patients with the best, the most appropriate and cost-effective approaches as available as possible. As Dr. Timmerman stated in a commentary (33), "Our job then, as thoracic oncologists, is neither to valiantly protect turf nor aggressively unseat the champion, but rather to carry out valid clinical scientific experiments (i.e., prospective clinical trials) to appropriately characterize the best role for each therapy." So, no port is good, but patient's survival and quality of life matter more.

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Footnote

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