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Mini-review

Stereotactic ablative radiotherapy in treatment of early-stage non-small cell lung cancer: Unsolved questions and frontiers ahead

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ABSTRACT

Stereotactic ablative radiotherapy (SABR) has been recognized as a standard alternative treatment to surgery for inoperable early stage non-small cell lung cancer (NSCLC). Guaranteed local control rates over 90% makes oncologists wonder whether SABR is qualified enough to challenge surgery in operable patients. The role of SABR for centrally located lesions would be another question because of the increased risk of severe toxic effect. Plenty of studies suggest that optimization of dose regimen and appropriate case selection would be helpful. Additionally, the effect of adjuvant therapy following SABR in selected patients is worth looking forward, given that it significantly reduced risk of recurrence after complete resection. A consensus about salvage treatment after SABR also needs, given the current diversity of options. Finally, witnessing the emergence of proton therapy and immunotherapy, we believe that the future of SABR lay behind these novel forms of treatment.

Introduction

Over the last decades, precise delivery of truly ablative radiation dose to target volume has become a reality with technological advances in tumor motion control, image guidance, and treatment planning system. Facilitated by these great progresses, stereotactic ablative radiotherapy (SABR, also called stereotactic body radiotherapy) has been widely used in treatment of early stage non-small cell lung cancer (NSCLC) and achieved promising efficacy. As the application of SABR is becoming increasingly widespread, controversy and questions have inevitably emerged. First, could SABR be introduced to operable patients in order to avoid surgical toxicity without impairment of tumor control, and what is the optimal range of corresponding biologically effective dose (BED)? Second, in management of centrally located NSCLC, would SABR still be appropriate and how could dose regimen and target delineation be adjusted? Third, which measures are necessary to further reduce risk of relapse and what salvage therapy is available after failure of SABR? Moreover, would the emergence of new techniques and therapy, like proton therapy and immunotherapy, beckons the new frontier of SABR? We here present a review to highlight these ongoing debates.

The controversy over application of SABR in operable patients

Lobectomy with dissection or sampling of mediastinal lymph nodes has been established as the standard treatment modality for early-stage NSCLC for decades and remains the most effective therapy. Fundamentally, a substantial proportion of patients are inoperable due to medical comorbidities, older age or poor performance status. For these frail patients, SABR can be provided as a noninvasive therapeutic alternative and guarantees a sufficient local control rate over 90% which is comparable to surgery [1–14]. Given its achievement for inoperable patients, a challenging subject was inspired: could SABR be introduced to operable patients?

Up to present, most research comparing SABR with surgery in early stage NSCLC are either phase I/II trails or retrospective analyses which enrolled inoperable and potentially operable patients. In the lack of randomized controlled clinical trials, systematic reviews were performed to compare SABR with surgery. In 2013,

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Francesca et al. reviewed 45 reports involving 3201 patients who underwent SABR for localized stage NSCLC and got a 2 year survival of 70% (95% CI: 67–72%) [15]. This date was numerically higher than a 68% (95% CI: 66–70%) 2 year survival of a surgical cohort derived from the IASLC database which included 2038 stage I patients. Given that SABR group was biased toward inoperable patients with less favorable prognoses, this study concluded that SABR potentially promised equivalent and even superior survival to surgery in operable patients.

Later studies controlled baseline characteristics in their adequate sample. It turned out that this conclusion remained convincing even when surgical treatment was restricted to lobectomy. A survival meta-analysis covering 23 surgery studies (7071 patients) and 40 SABR studies (4850 patients) provided evidence [16]. Although in initial unadjusted comparison SABR group was inferior to lobar resection in overall survival, the difference became insignificant after age and operability were controlled in regression analysis (hazard ratio [HR] = 0.52, 95% confidence interval [95% CI], 0.20–1.36). Another supporting study was a large Surveillance, Epidemiology, and End Results (SEER) analysis covering 9093 patients at median age of 75 years [14]. Unadjusted mortality at 3 years significantly favored lobectomy (25.0% vs. 45.1%, $p < 0.001$). Yet further propensity score-matched analysis, in which 8 independent variable including age and comorbidity score were adjusted and matched, presented similar overall survival between SABR and lobectomy cohorts again (adjusted hazard ratio [AHR], 1.01 [95% CI, 0.74–1.38]; $p = 0.94$). Both of these retrospective studies demonstrated comparable effect of lobectomy and SABR in similar patient group. Hence a prospective randomized comparison was unprecedentedly urged to provide a final conclusion (Details of these two studies and the following study are summarized in Table 1).

Finally a pooled analysis [17] of two randomized trials of STARS and ROSEL offered prospective evidence. This study enrolled and randomly assigned 31 and 27 patients to SABR and lobectomy respectively. Probably because of the small patient sample and short follow-up, the comparison fail to expose differences in disease control (recurrence-free survival: 86% vs. 80%; $p = 0.54$), whereas estimated survival at 3 years favored SABR group (95% vs. 79%; $p = 0.037$). Remarkably, previously unavailable toxicity comparison generated enlightening results. While only three (10%) grade 3 treatment-related adverse events were observed in SABR group, there were one (4%) surgery-related death and 12 (44%) patients suffering grade 3–4 treatment-related adverse events in lobectomy group. Apparently, the toxicity difference was more remarkable and probably made more contribution to the prolonged survival of SABR group.

Comparison across studies also confirmed the safety of SABR. While the procedure-related mortality of SABR was only 0.7% [18], mortality after surgery reached 5.4% even with minimally invasive techniques [19–21]. Given that severe surgical adverse events mostly occurred within 30–90 days after surgery, SABR hold its advantage in a relative short follow-up. The above mentioned SEER study demonstrated that the survival difference between SABR and lobectomy in elder patients was characterized by 2 phases [14]. SABR significantly improved survival during the initial 6 months after treatment; probably due to the risk of perioperative mortality was spared. Beyond six months, SABR lost its advantage and was overtaken by lobectomy thereafter. Given the robust effectiveness of lobectomy in long term, this study suggested that standard surgery could not be easily given up in operable patients, even with older ages.

Currently, large randomized clinical trial with long-term follow-up is still required to settle this question. Nevertheless, the relatively equal effectiveness of the two therapies and better safety of SABR in short term could be concluded based on existing researches. Therefore it is reasonable that SABR be recommended to high-risk operable patients other than common operable patients. However, sublobar resection could also reduce surgical risk for these patients [22,23]. So here comes another question: between SABR and sublobectomy, which one is the optimal treatment for high-risk operable patients with stage I NSCLC?

Unfortunately, the answer is even more blurring than the former one. Regardless that a great amount of studies suggested at least equivalent local control between the two modalities [24–29], highly convincing studies are nearly absent. The only inter-group randomized trial resolving this issue, RTOG 1021/ACOSOG Z4099, was prematurely closed and left no conclusion. In addition, several assignable flaws of current studies further weakened their reliability. For instance, in most studies specific operations were not discussed separately in comparison with SABR. Since anatomic segmentectomy achieved significantly better outcomes than wedge resection [30], stratification according to operations would be necessary. Furthermore, sublobarectomy is not always a compromised procedure. It could also be intentionally administrated as a parenchymal sparing option in healthy patients with small, peripheral, or indolent tumors. The ignorance of specific indication could enlarge selection bias favoring surgery. In a summary, to end this controversy, there is still a long way to go.

Table 1
Key studies comparing outcomes of SABR with surgery for early stage non-small cell lung cancer.

Authors	Type of study	HR or AHR for OS (SABR to surgery)	95% CI	p value
Zheng [16]	Meta-analysis	0.52	0.20–1.36	0.18
Shirvani [14]	SEER database analysis	1.01	0.74–1.38	0.94
Chang [17]	Pooled analysis of randomized trails	0.14	0.0017–1.190	0.037

Abbreviations: HR = hazard ratio; AHR = adjusted hazard ratio; CI = confidence interval.

The optimal BED for Stage-I NSCLC

SABR is characterized by hypofractionated-scheme, which means the significantly improved cumulative BED compared to conventional radiotherapy. Although radiation dose and fractionation varied across different regions and institutions, the threshold of BED in treatment of stage I NSCLC was generally set above 100 Gy [31,32]. Nevertheless, the optimal BED range was left unclear until Zhang et al. performed a meta-analysis to solve the question [33]. After reviewing 34 studies involving 2587 patients, they found medium BED (83.2–106 Gy, 3-year OS 63.5%) or medium to high BED (106–146 Gy, 3-year OS 63.2%) could guarantee a statistically significant OS benefit when compared with low BED (<83.2 Gy, 3-year OS 51.9%) or high BED (>146 Gy, 3-year OS 49.5%), respectively ($p \leq 0.004$). In addition, with dose escalation from medium to high BED, estimated 3-year cancer-specific survival was similar while obvious trend toward more severe adverse events appeared. These findings suggested that excessively high BED might be unnecessary and even impair survival of patients.

So, how could we choose between medium and medium to high BED? T-stage would be an appropriate reference. It is commonly recognized that outcomes of SABR for Stage IB disease is worse than Stage IA disease [34,35]. Interestingly, findings from a retrospective study enrolling patients under different dose regimens suggested that BED increasing could improve the inferior survival of Stage IB disease. In this study the difference of local control between Stage IA and Stage IB was significant when BED was below 100 Gy, while