



Stereotactic ablative radiotherapy for early-stage central lung tumors: status, challenges, and future considerations

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Stereotactic ablative radiotherapy: technological revolution or alternative treatments?

Different from general radiotherapy, stereotactic ablative radiation (SABR), also referred to as stereotactic body radiotherapy (SBRT), delivers very high radiation doses to restricted volumes using multiple, precisely-aimed radiotherapy beams, which has a better effect on survival and tumor control, and has gained substantial attention in recent years (1,2). In the latest National Comprehensive Cancer Network Clinical Practice Guidelines and the European Society for Medical Oncology Consensus, SABR is recommended as the most favorable therapeutic choice besides surgery for early-stage non-small cell lung cancer (NSCLC). Especially for medically-inoperable stage IA patients, SABR has been recommended as the initial treatment (3,4). Tekatli *et al.* reviewed and discussed the role of SABR and optimal approaches in central early-stage NSCLC in his latest review in *Lung Cancer* in September 2018 (5). That study investigated the following problems systematically: defining and nodal staging for central lung tumors, the toxicity of SABR, and the best strategy for treatment. In the concluding remarks, the applications of SABR in two different categories of central lung tumors were summarized: moderately central tumors and ultra-central tumors. Treatment risks seem to be acceptable in moderately-central tumors after SABR in more than three fractions because organs at risk (OAR) doses remain limited with recent techniques. However, in ultra-central

tumors where tumor-related risk factors are already present, conventional radiotherapy may be more appropriate because true OAR dose limits remain unknown. The highlight of that study was that it presented the advance and shortcomings of SABR in the stereotactic treatment of two different types of central lung tumors, and suggested future study aspects, which has great value and clinical significance in treating central lung tumors.

The application of SABR for tumors is undeniably a technological revolution, not only for radiotherapists, but also for surgeons. In the very beginning, to be conservative, SABR was considered as an alternative therapy for patients with inoperable disease or other cases (6). However, a large number of studies suggested that compared with surgery, SABR/SBRT had similar or even better survival and lower recurrence for patients with early NSCLC (7,8). Correspondingly, the guidelines now recommend SABR as the preferred option for medically inoperable patients with a peripherally located early-stage NSCLC. However, it does not influence the absolute status of surgery. Nevertheless, central tumors are considered difficult to be managed by many video-assisted thoracic surgery surgeons, which facilitates the development of SABR therapy for early-stage central tumors and also presents serious challenges (9). Which approach is better between SABR and surgery for patients with early-stage NSCLC, and whether different categories of central tumors have the same effect and toxicity with respect to SABR remain unclear. Hence,

further studies are needed to identify more reliable doses with normal organ tolerance and evaluate the risks and benefits, compared with surgery.

For early-stage central lung tumors: vista and dark clouds

A previous study held the opinion that central lung tumors were tumors either within or touching the 1-cm zone of the proximal bronchial tree (PBT) and separated subgroups of central tumors situated near the main stem bronchi (10). Interestingly, Tekatli *et al.* divided central lung tumors into two categories: “moderately central tumors” (tumors situated within 2 cm of PBT) and “ultra-central tumors” (tumors overlapping the trachea or mainstem bronchi) (5).

Surgery is the first choice for medically operable early-stage NSCLC. However, during the last decade, many studies showed that SABR may be a reasonable treatment choice for early-stage NSCLC, especially for patients who cannot tolerate surgery due to health status, advanced age, or other factors (11,12). A multicenter analysis showed that SABR served as a safe and effective treatment for aged patients who could not undergo surgery, not only improving survival, but preserving the quality of life (13,14). Yu revealed that patients with early-stage NSCLC treated with SABR had more favorable outcomes than those treated surgically (11,12). Additionally, SABR could improve quality of life, suggesting that quality of life could be a prognostic indicator of clinical outcomes (15). This might be because SABR was well tolerated with fewer complications, lower toxicity, and less damage in pulmonary function compared with other invasive treatments. In summary, both the improvement in survival and preservation of quality of life in patients with early-stage NSCLC indicated that SABR might be appealing in specific patient groups.

However, SABR has several potential risks. Chen *et al.* reported worse overall survival after SABR, compared with surgery in patients who could accept either treatment (SABR or surgery) (16). Previous analyses also revealed that the 5-year regional recurrence rate after SABR was approximately 12%, which was higher than that after surgery. This was because of the occult mediastinal lymph node metastases (16). Moreover, the toxicity of SABR remains an open question. Radiation-induced lesions include damage to cardiac structures, esophageal structures, and tracheal and bronchial structures, especially in patients with interstitial lung disease and idiopathic pulmonary fibrosis. Interestingly, in this study, not all patients could

benefit from SABR, and the location of tumors played a significant role in SABR treatment. Additionally, compared with ultra-central lung tumors, moderately central lung tumors had more safety in SABR delivery, which was consistent with the findings of a study by Donovan *et al.* (17). Therefore, how to balance the toxic effects of SABR in these special patients' needs further exploration.

Where to go?

NSCLC is one of the most commonly diagnosed and leading causes of cancer-related death among both men and women, worldwide. It consists largely of squamous cell carcinoma and adenocarcinoma. Compared with small cell carcinoma, NSCLC more frequently presents with localized disease at the time of diagnosis and, thus, is more often amenable to surgical resection, but less frequently responds to chemotherapy and radiotherapy. With the development and application of thin-layer computed tomography scans, an increasing number of patients with early-stage NSCLC were screened and diagnosed, providing an opportunity for the application of SABR. Recently, several studies investigated the use of SABR in patients with potentially operable peripheral early-stage NSCLC, establishing the role of SABR in peripheral early-stage NSCLC. Compared with peripheral tumors, most central lung tumors were diagnosed as squamous cell carcinoma, which thus, was considered to be related to poorer prognosis and more complicated operation demand of patients. The latest retrospective study indicated that squamous cell carcinoma histology was an independent prognostic indicator of worse survival in patients with early-stage NSCLC treated with SABR (18). Further, although cigarette smoking is etiologically related to the development of NSCLC in a large majority of cases, the latest studies have reported that fusions and point mutations of canonical oncogenes are often acquired in the early decades of life in nonsmoking patients with adenocarcinoma (19). With the increased use of epidermal growth factor receptor-tyrosine kinase inhibitors, the survival rate of patients with lung adenocarcinoma has improved substantially. However, few effective therapeutic targets for squamous cell carcinoma have been discovered.

However, consensus to support SBRT/SABR is lacking, and hence, the results related to this field are contradictory. The role of SABR in patients with early-stage lung tumors is still debatable. Data on the outcomes of SABR versus surgery in patients with early-stage NSCLC have increased in recent years (20). Several meta-analyses suggested that

surgery might still be more preferable than SABR in terms of overall survival and recurrence-free survival. However, for ultra-central lung tumors, SABR is feasible, but high doses to the PBT may be associated with severe toxicity (4,21). Therefore, the latest studies need to be critically highlighted, providing new insights into the application of SABR in patients with a centrally located lung tumor.

Toxicity to adjacent organs and the radiation strategy of SABR have restricted the development and use of SABR. The most common toxicities of SABR are tracheal and bronchial toxicity, cardiac toxicity, and esophageal toxicity. Moreover, both point dose and volume parameters need to be considered to reduce toxicities. Tekatli *et al.* reported that the maximum point dose was defined as 105% of the prescription dose, while the maximum dose to trachea and bronchi, heart, great vessels, and esophagus was 18 Gy to <4 cc, 32 Gy to <15 cc, 47 Gy to <10 cc, and 27.5 Gy to <4 cc, respectively (4,21).

Further studies are needed to search for more reliable normal organ dose and better-hypofractionated schemes to minimize the side effects in different categories of central lung tumors. In addition, magnetic resonance imaging-guided radiotherapy was used to provide more accurate estimates of delivered doses and is summarized in the supplemental data. However, simulation-based process analysis and design should be promoted through three-dimensional reconstruction and virtual reality, providing more accurate positioning and fewer side effects.

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Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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