Editorial

Perspectives on stereotactic body radiotherapy for early-stage non-small cell lung cancer: a maturing treatment modality

Chunhui Han

Department of Radiation Oncology, City of Hope National Medical Center, Duarte, CA, USA

Correspondence to: Chunhui Han, PhD. Department of Radiation Oncology, City of Hope National Medical Center, 1500 E Duarte Rd., Duarte, CA 91741, USA. Email: chan@coh.org.

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In 2017, The American Society for Radiation Oncology (ASTRO) published the long-awaited guideline on stereotactic body radiation therapy (SBRT) for early-stage non-small cell lung cancer (NSCLC) (1). This much needed document provides practical guidance to clinical radiation oncologists in making evidence-based decisions for the treatment of early-stage NSCLC patients under frequently complicated clinical scenarios. Subsequently in late 2017, after an updated literature search and a thorough review of the guideline content, the American Society of Clinical Oncology (ASCO) formally endorsed the ASTRO guideline with minor modifications (2). This ASCO endorsement, together with the associated modifications, makes the ASTRO guideline more suitable for a wider audience outside the discipline of radiation oncology. With endorsement by the two major medical societies to the SBRT guideline, it is appropriate at this time to look at the historical development of this revolutionary treatment modality, the role SBRT plays currently in the management of early-stage NSCLC, and what role it will play in the future.

The method of delivering high fractional dose to localized sites had long been successfully used in the treatment of intracranial lesions, in the form of intracranial stereotactic radiosurgery (SRS) (3). The use of SBRT for tumors in the thoracic and other extracranial sites started in the 1990s, when some pioneering centers applied the principles of intracranial stereotactic radiotherapy to the treatment of extracranial tumors, with encouraging clinical results (4-6). To ensure accurate dose delivery to extracranial sites, rigid body fixation devices with high setup accuracy (stereotactic body systems) and/or 3-dimensional (3D) image-guided patient setup techniques were used. Then, at the beginning of the 21st century, the team at Indiana University carried out a prospective phase I dose escalation clinical trial to evaluate the feasibility and toxicity of delivering high dose per fraction to medical inoperable early stage NSCLC patients (7,8). For a group of 47 patients, partial response was observed in all the T1 tumor patients, with complete response in more than 1/3 of the group. This and other study reports generated much interest and excitement in the radiation oncology community, and spurred numerous clinical trials across many centers. As a testament to the intense interest in this modality, in the first decade of this century, the Radiation Therapy Oncology Group (RTOG) initiated a series of clinical trials on SBRT treatment of early-stage NSCLC (9-12). In well-designed clinical trials, local recurrence was low, and local control was high with low toxicities observed.

The rapid growth of SBRT treatments for early-stage NSCLC patients benefited greatly from technological innovations in accurate target localization in the past couple of decades. Aligning the lung tumor target volume on the radiation treatment couch for SBRT is a much more difficult task than setting up the patient for intracranial

SRS, since there is no rigid mapping from the target position to external markers on the skin. In addition, the lung tumor typically has significant internal motion within the thorax due to constant breathing. Such technical difficulties limited this modality to a small number of large academic centers with adequate resources and experience in the early days. On the other hand, the simultaneous introduction of intensity modulated radiotherapy (IMRT) techniques into routine radiation treatments in the past decades stimulated rapid development of accurate target localization methods and novel image-guided patient setup techniques. To minimize respiratory tumor motion, abdominal compression techniques are now commonly used by placing a metal plate on the abdominal skin to limit diaphragm motion. However, even with abdominal compression, there could still be significant residual respiratory tumor motion, and tumor position relative to the thoracic bony structure could change on a daily basis (13). Four-dimensional computed tomography (4DCT) units are now widely available, and are commonly used to assess the internal tumor motion in respiratory cycles. Before each treatment fraction, image-guided patient setup techniques are commonly used to place the tumor target in the treatment position accurately. Such techniques include volumetric CT acquisition or planar image acquisition, use of implanted fiducial markers, and smart soft tissue-based image registration algorithms. During radiation beam delivery, respiratory gating or dynamic beam tracking are now available to further ensure accurate delivery to the target volume while sparing healthy lung tissue. Last but not least, development of novel IMRT delivery techniques such as helical tomotherapy and volumetric modulated arc therapy (VMAT) and smart plan optimization algorithms makes it possible to efficiently deliver highly focused dose to the target with sharp dose gradient in the surrounding tissue (14,15).

Despite being a non-invasive treatment modality for the treatment of early-stage NSCLC, the limitations and side effects of SBRT were gradually known as clinical data accumulated from clinical trials and clinical treatments. In the clinical trial conducted at the Indiana University, it was found that SBRT would incur higher risk of severe toxicity when the tumor was within 2 cm of the proximal tracheobronchial tree, when a three-fraction treatment scheme was used (16). Treating a tumor that is located close to the chest wall could lead to Grade-1, -2, or even -3 chest wall pain with certain risk of rib fracture (17). Radiation pneumonitis (RP) is a common side effect with SBRT treatment for early-stage NSCLC. Most patients will develop asymptomatic Grade-1 RP. However, the risk of developing Grade-2 or -3 RP is relatively low (18). Proximity of critical thoracic organs to the tumor target could present challenges in the treatment planning process. The ASTRO guideline recommends using a four- or five-fraction scheme and/or adhering to established dosimetric constraints when the tumor is located close to mediastinal structures including esophagus, heart, pericardium, and bronchial tree, to lower the risk of severe toxicities. And like all other radiotherapy treatments using ionizing radiation, there exists risks for radiation-induced secondary cancer occurrence in the thoracic region. However, such risks are minimal and are significantly overweighed by the potential curative benefits with SBRT treatments. Modern IMRT delivery techniques such as VMAT might not increase the radiation-induced secondary cancer occurrence risks compared to conventional 3D conformal radiotherapy delivery techniques (19).

Although there is strong evidence supporting the use of SBRT as an appropriate option for medically inoperable, peripheral early-stage (T1–2, N0) NSCLC patients, clinical scenarios often complicate clinical decision making in the management of early-stage NSCLC. Based on a comprehensive literature review of 172 published studies by the ASTRO task force team, the ASTRO guideline provides evidence-based recommendations targeting a comprehensive list of clinical scenarios, including medical operability, tumor size and location, presence of synchronous primary or multifocal tumors, and tumor recurrence. It should be noted that as high-quality clinical data are not always available or sufficient to each clinical scenario given the relatively short history in clinical application of this modality, the strength of recommendation and quality of existing evidence are listed accordingly in the ASTRO guideline, based on the GRADE methodology (20). While concurring with the key principles of the ASTRO guideline, the ASCO recommendation emphasizes the importance of decision making by a multidisciplinary medical team, especially for medically operable patients. The patient should be informed about existing treatment options, and about the efficacy and toxicities associated with each modality during the treatment decision making process.

As of today, SBRT has largely grown from being a highly technical and experimental way of delivering radiation to being one of the mainstream treatment options. The establishment of this modality for the management of

early-stage NSCLC patients was remarkable achievement thanks to tremendous amount of work done by intrepid pioneers in the past 2 decades, including radiation oncologists, radiobiologists, medical physicists, industry partners, and early participating patients. The history of its development represents a perfect paradigm for bringing new treatment concepts and methods into clinical practice. In the current era, the application of SBRT has expanded beyond the treatment of thoracic malignancies. It is now used in the treatment of liver malignancies as in the ongoing RTOG-1112 clinical trial, and in the treatment of oligometastatic lesions throughout the body (21). In the future, the efficacy of SBRT might be improved with biological guidance using novel molecular imaging methods in treatment planning and delivery (22). In the meantime, with accumulation of more clinical data and longer follow-up with this modality, clinicians will be able to update the guideline accordingly, and evaluate the long-term efficacy of SBRT in early-stage NSCLC treatments.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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