Editorial

Stereotactic ablative radiotherapy for stage I NSCLC: Successes and existing challenges

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Stereotactic ablative radiotherapy (SABR) has emerged as a standard treatment of peripherally located medically inoperable stage I non-small cell lung cancer (NSCLC) (1-5). With SABR, local control of primary tumors is greater than 90% in tumors up to 5 cm, and regional lymph node recurrence within the chest is low (5% to 10%). Distant metastasis remains a dominant pattern of failure (10% to 20%). SABR has been accepted by the National Comprehensive Cancer Network (NCCN) and is included in the NCCN treatment guidelines, and SABR is widely used (>75%) by radiation oncology centers, including community hospitals, according to a recent survey by the American Society for Radiation Oncology (ASTRO).

In this issue of the Journal of Thoracic Disease, Dr. Senan and colleagues reviewed the recent developments and controversies in SABR (6). Published data have consistently shown that SABR, when given at a biologically effective dose (BED) of greater than 100 Gy, achieves excellent local control with minimal toxicity, which is a significant improvement compared with conventional fractionated radiotherapy in stage I NSCLC (1-5). The dramatic improvement in local control could be due to the efficient killing of both radiosensitive and resistant cancer cells by ablative dose. Local control appears to depend on dose delivered and tumor size (1-5). As Dr. Senan and colleagues discussed, the dose delivered to the planning target volume (PTV) and isocenter can vary dramatically, depending on where the dose is prescribed (6). For example, a dose of 60 Gy prescribed to 60% of the isodose line could deliver 100 Gy to isocenter, and a dose of 60 Gy prescribed to isocenter could deliver only 57 Gy or even less to the PTV, depending on the location of the PTV. In addition, dose calculation algorithms used by treatment planning systems, such as pencil beam versus Monte Carlo calculation, can also cause dose variation (up to 15%). Therefore, it is very important to make sure that the PTV receives minimal dose coverage (the recommended BED is 100 Gy). To avoid missing the target and overdosing surrounding critical structures, image guidance (particularly volumetric image guidance) for each treatment and motion management in select cases with tumor motion greater than 1 cm are highly recommended (7).

SABR is a double-edged sword that can kill cancer cells but can also damage surrounding critical structures (2). Therefore, well-designed SABR requires a sharp dose gradient from ablative dose to tolerable dose. In addition, case selection and appropriate SABR dose regimens based on target location are crucial to reduce toxicity. Critical structures such as the esophagus, bronchial

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tree, spinal cord, brachial plexus, and trachea should not receive the ablative dose. Therefore, hilar lymph nodes and mediastinal lymph nodes should not be treated with SABR owing to their proximity to these critical structures. For lung parenchyma lesions close to these critical structures, individualized treatment planning for dose distribution (4) and/or reduced dose fraction size should be considered (8). Dr. Lagerwaard and colleagues proposed adaptive dose regimens that appeared to achieve promising outcomes (8). Dr. Xia and colleagues reported that 70 Gy prescribed to the gross tumor volume (GTV) in 10 fractions was tolerable in central lesions (9). Using 50 Gy in 4 fractions, we tailored the dose distribution to deliver the conformal dose to the target and avoid delivering the ablative dose to surrounding critical structures using 4-dimensional computed tomography (CT)-based SABR panning, individualized dose-distribution techniques, and on-board volumetric (cone-beam CT or CT on rails) image verification for each fraction in central lesions, promising local control and acceptable toxicity would be achieved (4). For recurrent or new primary isolated lung parenchyma disease (< 4 cm) in patients who received prior conventional fractionated radiotherapy to chest, SABR achieved excellent local control (>90%), although toxicity was higher than patients who never received prior radiotherapy to chest but could be predicted using a clinical index model (10,11).

The role of SABR in patients without a pathologically confirmed diagnosis remains debatable. In most centers in the United States, SABR is not considered if there is no pathological confirmation for suspected new primary stage I NSCLC. However, Dr. Senan and colleagues note that the false-positive rate is less than 4.5% in The Netherlands, and they feel that SABR is justified in select cases without pathological confirmation when the false-positive rate is low. Treating physicians need to know the false-positive rate with clinical diagnosis in their region and discusstreatment options with their patients before considering SABR without pathological confirmation.

The rate of lymph node recurrence after SABR is between 5% and 10%, although these lymph nodes were not treated. This incidence rate is comparable with the rate of recurrence in surgical resection. The modern staging workup, including positron-emission tomography (PET)/CT, endobronchial ultrasound (EBUS), and mediastinoscopy has helped to stage these lymph nodes more accurately, and available data support treating the primary lesion only, particularly for small lesions located peripherally.

Follow-up images after SABR remain controversial owing to abnormal consolidation of lung parenchyma after SABR and residual PET activity. However, recent post-SABR PET images showed the predictive role of PET for local and regional recurrence and distant metastasis (12). A high post-SABR standardized uptake value (SUV) (>5) more than 3 months after SABR should raise suspicion for local recurrence and close follow-up is indicated. If the SUV remains high with serial images, biopsy should be considered to confirm the local recurrence (12).

The role of SABR in operable stage I NSCLC is promising, based on published data and SABR is being investigated in ongoing phase III clinical studies. In addition, distant metastasis remains a dominate pattern of failure in this group of patients after SABR, and clinical studies for adjuvant chemotherapy and for target treatment are ongoing. The identification of a molecular marker to predict distant metastasis would help clinicians decide which patients need adjuvant systemic treatment.

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