Preface

The current and future faces of stereotactic body radiation therapy for thoracic malignancies

The field of radiation oncology has undergone a shift in practice towards hypofractionation, a movement that has seen increasing momentum over the past decade. This trend responds in part to a need that has been identified throughout oncology for maximally effective and efficient allocation of resources, cost containment, and further side effect mitigation. Specific to the field of radiation oncology, hypofractionation also plays an integral role in dose escalation and improved tumor control. In one of its most "extreme" forms, hypofractionation with stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), allows for the delivery of few large fractions of radiation (generally 1–5 fractions) to a finite tumor volume (most commonly ≤5 cm) that is accurately and reproducibly localized relative to a known three-dimensional reference system (1). With the rapid dose fall-off achievable with SBRT, the target can receive an ultra-high biological effective dose (BED) not previously achievable with traditional methods of external beam radiotherapy delivery, while the surrounding normal structures are often more effectively spared exposure to excess irradiation dose, resulting in an improved therapeutic ratio (2).

SBRT has taken on a role of particular significance in the treatment of early stage non-small cell lung cancer (ES-NSCLC), in which the delivery of a BED equal to or greater than 100 Gy to the gross tumor volume improves both local control and overall survival outcomes compared with regimens using lower BEDs (3). Common to the development of any novel technology, an initial period of learning during which troubleshooting, modifications, and optimization took place in the preliminary forays into ultrahypofractionated radiotherapy. Early investigations of SBRT for ES-NSCLC were met with challenges in understanding optimal clinical margins, dose-fractionation schemas, dose heterogeneity and coverage, image guidance approaches, and respiratory motion management techniques. In addition, the serious adverse event profile of early reports was high, leading to the recognition of the potential morbidities associated with certain dose regimens delivered in close proximity to central thoracic structures (4).

Robust efforts were subsequently undertaken to better understand these early results, and great strides have since been made in optimizing treatment delivery strategies for SBRT, evident in the number and breadth of prospective investigations that have recently been reported and/or are ongoing. For tumors considered to be in prohibitively close proximity to critical central structures, such as for "ultra-central" tumors, utilizing alternate SBRT dosing schemas with more than the original 3- or even 5-fraction approach while maintaining a target BED of ≥100 Gy has been studied prospectively with promising outcomes (often termed "SBRT-like" treatment) (5-7). In addition, dose-volume constraints specific to SBRT and SBRT-like treatments for both central and peripheral lung lesions continue to evolve using dosimetric data from these and other investigations, which will provide important practical guidelines to assist in further minimizing treatment-related morbidities.

Great strides have been made in optimizing the delivery of SBRT in the lungs. Increased awareness of the special considerations necessary for SBRT delivery of tumor movement with respiratory motion, precise tumor delineation, prescription specification, image guidance algorithms, and dose conformality and heterogeneity goals have all improved our ability to deliver a more safe and effective treatment (8,9).

With the ability to safely escalate the BED to the tumor, local control rates have been found in multiple studies to be equivalent to or better than those for a sublobar or wedge resection, making SBRT an important alternate treatment option for patients who are medically inoperable or are borderline surgical candidates (10). In addition, the side effect profile of SBRT is generally far more palatable compared with the perioperative morbidity associated with surgery, which has spurred increasing interest in the use of SBRT as definitive management even in the operable setting. The role of SBRT in medically operable ES-NSCLC remains a controversial topic, although recent findings of a combined analysis of two randomize trials addressing this question in the medically operable setting suggest that SBRT likely provides at least near-equivalent tumor control and survival outcomes compared with lobectomy with a more favorable toxicity profile (11). In addition, long-term data from multiple prospective SBRT trials are emerging and thus far demonstrate that early clinical outcomes of local disease control and toxicity are maintained with continued follow-up (12-14). At the present time, lobectomy remains the standard

definitive treatment for medically operable ES-NSCLC; however, the role of definitive SBRT for these patients is evolving, and this modality may prove to become a standard primary treatment option for ES-NSCLC as the literature evolves.

SBRT applications in the lung have also begun to spread beyond ES-NSCLC to include lung malignancies not previously included in the traditional understanding of allowable limits. For example, primary tumors larger than the previously accepted size limit of 5 cm appear amenable to and effectively treated with SBRT (15,16). In the salvage setting after surgical or conventionally fractionated radiotherapy failures, SBRT may play an important role given its ability to optimally spare adjacent normal tissues. Additionally, given the demonstrated success in establishing the utility of SBRT for NSCLC, initial investigations into the possible applications of SBRT in the setting of small cell lung cancer have been performed and appear encouraging (17,18).

SBRT may also be considered outside of the primary lung cancer setting to provide a clinical progression-free survival benefit in the treatment of oligoprogressive or oligometastatic disease. In this setting, SBRT may impart minimal toxicity while still providing local control to patients with limited metastatic disease to prevent or improve symptoms, decrease the risk of additional disease dissemination to other distant sites, achieve durable local control for all involved sites, delay the need to switch or restart systemic therapy, and potentially impart a survival advantage (19-21).

Immunotherapy is a topic of rapidly-growing interest in the field of oncology (22). Preliminary data have shown that in combination with large doses of radiotherapy as delivered in stereotactic treatments, the immune response generated by hypofractionated radiation may be potentiated by combination immunotherapy (23). In combination with immunotherapy, SBRT may most optimally result in an immune response that can enhance the tumoricidal response not only locally, but also systemically.

We are in the midst of an exciting time of rapid advances and innovation for SBRT across multiple disease sites, but particularly for thoracic malignancies. The role of SBRT for lung cancer continues to evolve and grow. For ES-NSCLC, treatment paradigm and delivery techniques are undergoing refinement to deliver SBRT in the most effective and safe manner achievable. Information gathered from ongoing and future studies will continue to guide our field on a path that will undoubtedly see the continued expansion of the applications of SBRT in multiple clinical settings.

In this focused issue of *Translational Lung Cancer Research*, these evolving issues in SBRT are reviewed by experts in the field of thoracic radiation oncology. We thank the journal editors for the opportunity to be guest editors of this timely focused issue, and we hope that the readers enjoy the topics discussed and find relevance and opportunities for applications in their current clinical practices and research pursuits.

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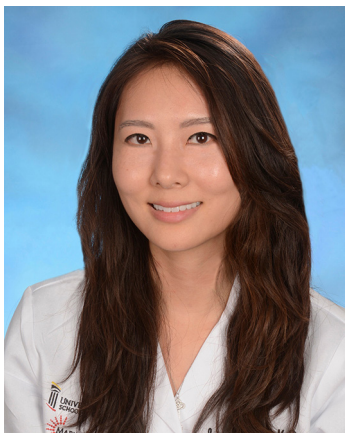

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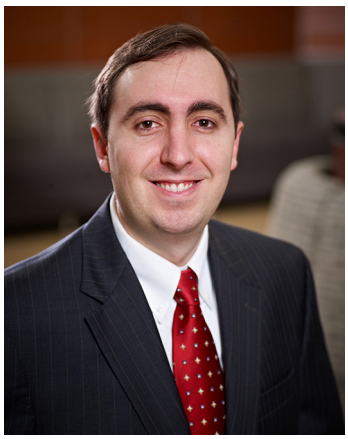

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