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Abstract
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An International Consensus on the Design of Prospective Clinical-Translational Trials in Spatially Fractionated Radiation Therapy

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Abstract

Objective: Spatially fractionated radiation therapy (SFRT), the treatment of tumors with intentionally non-uniform dose, is a complex radiotherapy concept of increasing interest in clinical and experimental radiation oncology. Pilot studies show high tumor responses and low toxicity rates in patients with bulky metastatic and primary malignancies. However, SFRT technologies, techniques and dosing concepts are currently highly variable, making the design of clinical trials challenging. No prospective randomized or multi-institutional clinical trials of SFRT (as the hallmark of clinical validation) have been conducted to date. Agreement on complex SFRT clinical trial design parameters is essential to enable broad participation and successful accrual in future SFRT trials. We aimed to develop a common approach and consensus guidelines for multi-institutional SFRT clinical trial design in the most commonly treated primary sites, head and neck (H&N) cancer and soft tissue sarcoma (STS), to enhance feasibility of multi-center trials.

Methods: For both H&N cancer and STS, a formal consensus effort was established and disease-specific Expert Panels were convened. Trial design criteria comprised the full spectrum of clinical trial parameters: eligibility/exclusions, SFRT technology/technique, dose/fractionation parameters, target and normal tissue parameters, systemic therapies, pre- and post-therapy investigations, on-treatment evaluations for tumor control, toxicity and quality-of-life, and translational science considerations. Iterative appropriateness rank voting, Expert Panel consensus discussions, and open comment posting were employed for consensus development.

Results: Consensus for both disease sites was overall high to moderate. Consensus in H&N cancer recommended inclusion of newly diagnosed patients with squamous cell carcinoma and stage N3 bulky lymph nodes of oropharynx, nasopharynx and larynx primary sites, excluding salivary and paranasal sinus tumors. SFRT to bulky lymph nodes (not the primary site) was recommended to a GRID SFRT dose of 15 Gy in 1 fraction to the GTV (without a margin), and followed by conventionally fractionated standard-of-care (SOC) comprehensive definitive-dose radiation therapy. Concurrent chemotherapy was recommended according to SOC.

In STS, eligibility included patients with stage IB-IIIB, >8 cm, grade 2-3 extremity STS in the preoperative setting with or without preceding neoadjuvant chemotherapy. Preoperative GRID SFRT of 15-18 Gy in 1 fraction to the GTV (without a margin) is followed by SOC preoperative doses in addition to the SFRT dose.

For both disease sites, standardization and reporting of the dosimetric and physics parameters describing the dose heterogeneity was emphasized. Prospective collection of pre, intra- and post-therapy translational correlates for biological endpoints were considered essential for trial design. Prospective functional/molecular imaging was encouraged to alleviate the challenges in obtaining direct tumor tissue based markers during and post radiation therapy. Pre-, intra- and post-treatment response and toxicity evaluations follow the SOC. Quality-of-life assessments and patient-reported outcomes were highly recommended. The consensus recommended that the addition of immunotherapy be reserved for future trials after the initial multi-institutional trials, which first add SFRT to the current SOC regimens.

Conclusion: This consensus provides a basis for cohesive design of prospective multi-institutional clinical trials based on an in-advance agreement among potential investigators and the SFRT community on fundamental and clinical trial criteria for prospective multi-institutional investigations in specific primary tumors. This approach may hold the promise of more streamlined trial design, better trial execution, and an overall advancement in our understanding of the applicability of SFRT to clinical care through rigorous clinical investigations.