Draft for Comment:

Consensus Guideline Recommendations for the Design of Clinical Trials in Spatially Fractionated Radiation Therapy for Soft Tissue Sarcoma

Introduction

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 response and low toxicity with SFRT in patients treated with palliative or curative intent for bulky tumors, including sarcoma (1-9). However, no prospective randomized or multi-institutional clinical trials of SFRT have been conducted. Consensus on complex SFRT clinical trial design parameters is essential to enable broad participation and successful accrual in future SFRT trials, while facilitating trial designs that incorporate relevant physics metrics as well as enable translational studies of SFRT. Such consensus is challenged by the highly variable SFRT technologies and techniques, the complex dosing concepts, and the overall still limited clinical experience with SFRT in the definitive treatment of specific *primary* malignancies. The purpose of this guideline was to develop a common approach for future multi-institutional clinical trial design in SFRT specific to soft tissue sarcoma.

Following an initial literature review, the consensus was developed by a group of recognized SFRT experts who rated a comprehensive set of clinical trial design categories (detailed in the guideline). Anonymized voting results were shared among a Sarcoma specific Expert Panel and iteratively reviewed and discussed, followed by a repeat literature collection and review, and the development of the draft recommendations presented here.

This document represents draft consensus guideline recommendations that are posted for review and comment. These draft recommendations are not intended to be reproduced, disseminated or used as a clinical treatment guideline. For details on the consensus process, see the link on the Radiosurgery Society website, www.therss.org/Clinical-Trials.

SFRT Clinical Trial Design Consensus Guideline for Soft Tissue Sarcoma

The SFRT clinical trial design recommendations are guided by studies of multiple disease sites containing sarcoma patients and by disease-specific studies of cohorts that include only sarcoma patients. The clinical experience to date consists of two published studies with cohorts of largely palliatively treated patients that contain patients with soft tissue sarcoma (1,

2). *Disease-specific* series of definitively treated patients with sarcoma have been presented in abstract form (4, 5), and one outcome study (6) was recently published. Collectively these clinical cohorts provide consistent pilot experience that was considered in conjunction with the clinician, physicist and biologist experience of the multidisciplinary Expert Panel for SFRT Clinical Trials in Sarcoma.

Eligible disease sites

A clinical trial of SFRT and sarcoma should include predominantly soft-tissue sarcomas of the extremities, the most common presentation, which also have the most pilot experience. The less common head and neck region and intraabdominal/retroperitoneal disease sites were considered to add unnecessary variability for the interpretation of outcomes in a clinical trial (high consensus).

Eligibility/Exclusion criteria: Disease Stage, Tumor Size/Extent/invasion

Enrolment of patients with unresectable extremity soft tissue sarcomas, stages IB–IIIB, with tumor size of more than 8 cm, who are planned for a treatment regimen including pre-operative radiation, is recommended (high consensus). It may be appropriate to enroll patients with lymph node involvement, which is overall uncommon (high consensus).

Eligibility/Exclusion criteria: Histology

Patients with undifferentiated pleomorphic sarcoma, myxoid liposarcoma, leiomyosarcoma and osteosarcoma should be considered eligible (high consensus). This eligibility profile reflects that of major randomized prior trials in sarcoma with conventional radiation (10-12). The Expert Panel considered it important to maintain a patient population that is consistent with these trial cohorts, in order to allow comparison of outcomes of SFRT with those in prior trials.

Grade 2-3 histologies are eligible. Grade 1 sarcoma and other histologies, including rhabdomyosarcoma, Ewing's sarcoma, chondrosarcoma, Kaposi's sarcoma and angiosarcoma should be excluded (high consensus). While some of these histologies have been treated with SFRT, their different natural disease course and rarity was deemed to add confounding variability to a clinical trial of SFRT cohort.

Eligibility/Exclusion criteria: Prior treatment

Recurrent sarcomas after either previous resection or previous radiation therapy should be excluded to prevent confounding variables within a clinical trial.

Eligibility/Exclusion criteria: Patient factors (age, toxicity risk factors)

Patients with scleroderma who may have a high toxicity risk from radiation, particularly in subcutaneous and skin regions, should be excluded from a clinical trial (high consensus).

Patient age should follow general trial criteria, and an upper age limitation of 85 years may be appropriate (moderate consensus).

Endpoints

The feasibility of delivering SFRT according to the dosimetric and physics specifications (13) (see sections Radiation Therapy: SFRT Dose), and response metrics including primary tumor response, classified by imaging and by pathology response criteria, and resectability are suitable potential primary endpoints. Local recurrence-free, metastasis-free and overall survival, and quality of life outcomes present additional clinical trial endpoints.

Stratifications

Patients should be stratified by tumor bulk, using largest imaging-based tumor diameter, of ≤12 cm vs. >12 cm. If neoadjuvant chemotherapy is used (see section *Concurrent systemic therapy: Agents and timing*), then neoadjuvant chemotherapy vs. no chemotherapy should be stratified, as both regimens are in clinical use.

Pre-treatment Evaluations (clinical, imaging, histologic investigations)

Standard workup with, preferably MRI and or CT of the involved site was recommended. For metastatic workup chest abdomen and pelvis CT and PET/CT were recommended.

Radiation Therapy: SFRT Dose

A dose range of 15 to 18 Gy in 1 fraction was considered appropriate as the dosing regimen for clinical trials (high consensus). The EUD of the SFRT regimen should be reported for tumor and normal tissues.

Radiation Therapy: SFRT Target volume

The target volume for SFRT, based on clinical experience (4-6), is the GTV of the primary tumor, without an additional margin.

Radiation therapy – SFRT: OAR constraints

Consideration should be given to exclude sensitive neural structures such as brachioplexus from the SFRT target volume and the beam path (high consensus), recognizing that this may not be possible if these structures are involved with tumor.

Radiation Therapy: SFRT: SFRT technique

For an initial clinical trial, it is recommended that GRID therapy be the technology of choice, based on available clinical experience with GRID therapy (1, 2, 4-6) and the currently insufficient clinical experience with Lattice therapy in sarcoma (high consensus). Lattice therapy may be appropriate in future trials.

Radiation therapy – Conventional ERT: Dose and technique

There is high consensus that the conventional ERT dose, following the SFRT fraction, should be

50 Gy in 25-28 fractions to the PTV, per RTOG trial regimens using IMRT or 3D Conformal technique (11, 12). As in standard-of-care radiotherapy, treatment to the entire extremity circumference is to be avoided (high consensus).

Radiation therapy – Conventional ERT: OAR constraints

Conventional dose constraints to critical normal tissues should be applied. The dose contribution from the SFRT should not be counted towards the dose constraints (moderate consensus). If there is concern regarding normal tissue doses, the dose to normal structures should be reduced *upfront* by adjusting the dose coverage in the SFRT fraction.

On-therapy Evaluations and feasibility

On-treatment evaluations should consist in standard weekly toxicity assessments, quality-of-life assessments and patient reported outcomes. Specimen collection of blood and urine multiple times during radiation therapy for the design of translational correlative of studies to investigate the underlying mechanisms should be considered. While serial blood draws during the treatment course are not standard-of-care in radiation therapy for sarcoma, collection of blood and urine for correlative studies is considered acceptable and feasible for a clinical trial (high consensus). Tumor biopsies during the treatment course for the purpose of correlative studies was considered to be not clinically feasible (high consensus).

Concurrent systemic therapy: Agents and timing

Concurrent chemotherapy, delivered *during* the radiation therapy course, is not permitted in an initial clinical trial (high consensus). Concurrent chemotherapy is inconsistently and not widely used in current clinical practice, providing a rationale for the omission of concurrent chemotherapy, as concurrent chemotherapy may introduce confounding variables in the interpretation of response, toxicity and overall outcome results.

Any neoadjuvant prior to the radiation therapy course and adjuvant chemotherapy following radiation therapy completion is acceptable. Agents considered acceptable in standard-of-care practice are allowed in clinical trials (high consensus).

Concurrent systemic therapy: Immunotherapy

Immunotherapy is not permitted initial clinical trial in order to reduce variables that may confound endpoints in an initial clinical trial (high consensus). Immunotherapy should be studied in a subsequent trial.

Post-radiation Therapy (preoperative) Evaluations: Response assessment

For post-radiation therapy, preoperative response assessment, MRI, assessment of imaging response per RECIST criteria and quantitative assessment of tumor necrosis (>90% necrosis) along with standard clinical examination was recommended with high consensus. A time interval of 8-12 weeks post-radiation is recommended for post-radiation/preoperative response

assessment. These assessments should be done in conjunction with patient reported outcome assessments that include QOL (high consensus).

Surgical Evaluation, pathologic response

Pathologic tumor response, as carried out routinely in standard of care, provides as an important outcome assessment for SFRT response in clinical trials for soft tissue sarcoma. The surgical specimen further provides an important potential resource for the prospective study of molecular markers in both the irradiated tumor and normal tissue.

In the post-radiation-therapy assessment, criteria that should be collected are resectability (R0 vs R1 resection) and by pathologic criteria of tumor response, including quantitative histologic assessment of necrosis of >90% (high consensus).

Post-therapy Evaluations (after completion of all therapy)

Consensus on response and toxicity evaluations after completion of all therapies was high, and follows the general standard of care. Follow-up evaluations should occur every 3-4 months for the first 2 years post-therapy; every 6 months for 3 years, and subsequently yearly. These evaluations consist in clinical examination combined with imaging, generally MRI, specific to the primary site of the sarcoma, and CT imaging as clinically indicated. History and clinical exam are indispensable for the assessment of function and toxicity. Patient reported outcomes, including quality-of-life assessments should be combined with the routine post-therapy evaluations.

Knowledge Gaps that May be Addressed through SFRT Clinical Trials in sarcoma

Clinical knowledge gaps identified by consensus voters and Expert Panel include a better understanding of the effectiveness of SFRT in increasing pathologic CR rates; potential local and systemic effects; and local long term toxicity of SFRT in sarcoma.

Knowledge gaps in the *physics* of SFRT focus on further understanding of appropriate field set up, treatment delivery and quality assurance.

Knowledge gaps in area of *biology* include the wide range of biologic effect of SFRT.

Conclusion

SFRT clinical trials in Sarcoma are feasible based on the clinical experience provided by the pilot studies. Recommendations for eligibility aim to establish a uniform patient cohort of bulky extremity sarcomas who are planned to be treated with preoperative radiation with or without

neoadjuvant chemotherapy. Less common trunk and other primary site locations and less common histologies should be excluded to support adequate patient enrollment while minimizing confounding variables that may hamper the interpretation of the outcome results. GRID technology is favored over Lattice radiotherapy based the technologies used in the current pilot studies. A single SFRT fraction of 15-18 Gy is recommended, and is followed by full-dose conventional (uniform) preoperative external beam radiation therapy. Reporting of inhomogeneity dose parameters according to recent SFRT physics guidelines, particularly EUD is highly recommended to allow data interpretation, plan comparison and correlation of dose parameters with clinical outcome. Chemotherapy agents that are used in standard-of-care management are permitted for the use of neoadjuvant chemotherapy. Concurrent Chemotherapy is not permitted. Pre-therapy, on-therapy and post-therapy investigations to assess tumor control and toxicity endpoints generally follow the standard of care and should include patient reported outcomes. Specimen collection (blood, urine), synchronized prospectively with the treatment course, for translational correlative science studies is highly recommended. Systematic post-radiation pre-operative imaging assessment and pathologic tumor response assessment from definitive resection follow the standard criteria and include quantitative assessment of tumor necrosis. While pre-therapy (diagnostic) biopsies and tissue procurement from the surgical resection specimens provide a potential resource for the prospective study of correlative molecular tissue markers, tumor tissue collection during the radiation therapy course for correlative science is challenging.

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