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Guidelines for the Use of Hadron Radiation Therapy in NCI-Sponsored Cooperative Group Clinical Trials Updated Summer 2019

The earlier proton radiation therapy (PRT) guidelines were created by the National Cancer Institute (NCI) in 2007, 2010, and 2012. This document represents the latest revision. There are potential advantages to patients from PRT but substantial concerns persist as protons are more sensitive than photons to uncertainties in the processes of planning and delivering radiation therapy. Hence there is a need for approvals, protocol-specific credentialing, and quality assurance requirements that are specific for PRT. The guidelines below are intended to ensure that PRT is employed safely and consistently in the setting of multi-institutional cooperative group clinical trials so that neither patient safety nor the study is compromised. These guidelines only specify the requirements for any facility that uses PRT to treat patients on any applicable NCI-supported clinical trial. They are not to be construed as prescriptive of standards of care. Other hadron therapies will be treated in a similar fashion in the future, once more biological and clinical data support their use.

Guidelines:

1. Prior to an institution being allowed to enroll any patients on an NCI-funded cooperative group protocol that requires or allows PRT, that institution must be approved[†] for the use of protons in clinical trials. This approval process consists of:
 - a. Completion of the [proton facility questionnaire](#)
 - b. Annual monitoring of the proton reference beam calibrations by the IROC Houston QA Center.
 - c. Ability to electronically transfer treatment plans using the latest edition of the [DICOM standard](#)
 - d. Verification of clinical CT calibration and stopping power conversion curve(s)
 - e. Successful irradiation of the [IROC's baseline proton phantoms](#) with clinically appropriate treatment

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- f. Successful completion of an on-site dosimetry review visit, to occur only after the center has been routinely treating patients for a minimum of 4-6 months and no fewer than 3 anatomical disease sites, and completion of the site visit report by IROC Houston recommending approval.

IROC Houston will coordinate the completion of the approval processes in conjunction with the other IROC quality assurance offices.

It is recommended that institutions complete an output check, CT calibration verification, and at least one phantom irradiation before the start of patient treatment.

If an institution modifies an approved delivery methods and commissions a new delivery technique (e.g. spot scanning to continuous scanning, or fixed beam to arc proton therapy), the institution is required to repeat the proton H&N phantom irradiation.

As technology develops, such as high dose rate delivery, institutions should ensure proper determination of dose rate and verify dose delivery. IROC will verify beam characteristics.

If an institution commissions a new treatment planning system, algorithm, or a major dose calculation engine upgrade, the institution should recalculate the proton H&N phantom dose and submit to IROC for evaluation.

2. An NCI multi-institutional clinical trial may require specific credentialing† procedures for the PRT technique to be used on the protocol. The specific credentialing procedures will be developed through interactions of the cooperative clinical trial groups and QA centers and will be detailed within the protocol. The credentialing procedures may include but are not limited to:

- a. Site-specific phantom irradiation
- b. Evidence that the institution has previously treated patients in the specific manner required by the protocol
- c. Completion of a protocol-specific knowledge assessment
- d. Completion of a protocol-specific electronic benchmark case

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e. Clinical and technical rapid review of patient treatment plans for each patient enrolled during credentialing (trials may require rapid review beyond the credentialing period)

f. Completion of the IGRT process verification

† Note: "Approval" as stated above refers to an institution's "general" ability to use and deliver PRT, as evaluated by IROC Houston, for NCI funded clinical trials. Whereas, "credentialing" refers to IROC evaluating an institution's ability to deliver PRT in a specific manner or to a specific target, as defined by protocol specifications.

3. The institution is expected to have established a comprehensive PRT QA program with tests performed on a periodic basis that can be evaluated by the IROC Houston and the appropriate protocol QA centers. This program should ensure consistency in PRT dose delivery and target localization accuracy for patients treated on NCI-sponsored clinical trials.

4. Protocols permitting the use of PRT must clearly state the rationale for the use of PRT and the conditions under which PRT is allowed in order to maintain dosimetric consistency (e.g. motion control techniques or image guidance requirements).

5. Every protocol that allows PRT must name a radiation oncologist as well as a physicist, both with applicable PRT expertise, who will be responsible for ensuring that the protocol prior to submission to the NCI incorporates appropriate dose and volume terminology, specific constraints to targets and organs at risk, and protocol-specific QA needs. The PRT radiation oncologist and physicist may but need not be named on the protocol cover page at the discretion of the primary protocol PI, but shall, at a minimum, be named within the body of the protocol as having contributed to the PRT specifications of the protocol and be available for questions relating to those specifications.

6. The IAEA TRS 398 protocol in conjunction with ICRU 78 recommendations are recommended for beam calibration and dose specification.

7. Currently, proton doses shall be expressed in units of Gray (Gy(RBE)), which is equal to the absorbed dose times the conventional scaling factor of 1.1. The radiobiological effective dose is a complex biological function. The NCI expects this aspect of dose to be under active investigation (e.g. linear energy transfer (LET) optimization, molecular biology-based modeling, and

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other areas of advanced radiobiology research) and has the long-term goal of moving the scaled physical dose prescription to a robust biological dose prescription.

8. The mathematical function(s) and process for converting the institutional CT-based treatment planning system “CT number” (for the institution- and protocol-specific CT scanners and parameters used for proton dose calculation) to proton “relative stopping power” must be established and documented at each institution. The institution must have implemented a QA program for its CT imaging system(s). This process may be reviewed during the IROC Houston site visit or by remote review of the written procedures and records. For new patient imaging modalities (e.g. dual-energy CT, proton radiography, synthetic MR), a separate review is required.

9. Doses will be specified to volumes using the standard nomenclature, i.e. GTV, CTV/ITV, and PTV as defined in ICRU Reports 50, 62, and 78. The GTV, CTV, and PTV shall be defined identically for protons and photons. Every protocol that allows PRT must explicitly address issues such as, but not limited to: inter- and intra-fractional setup uncertainties (IM and SM), range uncertainties, and distal penumbra. In proton treatment plans, dose coverage criteria should be evaluated using the CTV with protocol-specific robust analysis to account for uncertainties in patient position and beam range (e.g. 3%/3mm or 5%/5mm), and shall define the evaluation criteria specific to the disease site (e.g. the worst case V95, the nominal (baseline plan prior to robustness analysis) and the worst case minimum dose to 0.04 cc, nominal hot spots to critical structures).* It is recommended that protocols request OARs be presented in a manner demonstrative of formal robustness analysis as well (e.g., either DVH or best and worst case tables of OAR worst doses to 0.04 cc are shown explicitly). In proton plans designed using robustness optimization, the nominal plan should be used for OAR dose reporting (e.g., V20, minimum dose to 0.04 cc etc.).

Although a photon-concept PTV is not used for proton treatment planning, it should be created for evaluation and reporting purposes.

10. The protocol must provide a clear description of the dose prescription and dose rate requirements, as well as dose heterogeneity permitted in the target. The protocol must also specify the volume of the target to be covered by the prescription dose, as well as maximum and minimum dose constraints.

11. The protocol should specify whether double scattering, uniform scanning, or intensity-modulated proton therapy (IMPT) are allowed. IMPT plans shall include a definition of allowable optimization methods, including single-field

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optimized (SFO) plans (including simultaneous integrated boosts (SIB)) or multi-field optimized plans (MFO).

12. For protocols in disease sites with a large amount of heterogeneity (e.g. lung), Monte Carlo is required for the final dose calculation.

13. The protocol must explicitly address the localization and immobilization of both the patient and the target. The designated QA Center, with the assistance of the designated protocol proton experts, should assess the appropriateness of localization and immobilization systems for the individual protocol.** Image guidance (e.g. surface imaging, kV imaging, cone beam CT (CBCT), CT-on-rails, MRI, PET) should be performed daily. Certain clinical situations may require more intensive image guidance.

14. Tissue volumes with a possibility of large motion require that the dosimetric effect of motion be mitigated by a verified procedure to ensure accurate dose delivery to the intended volume. Results of the motion management procedure(s) should account for both inter- and intra-fraction motion. An institution's capability to deliver these treatments should be assessed with IROC anthropomorphic moving phantom irradiations.**

15. Patient anatomical and physiological changes that may perturb the proton beam range during a fraction or over the course of treatment should be assessed through the course of treatment and, if necessary, accounted for by repeating the planning process.**

* Robustness Analysis for External Beam Radiation Therapy Treatment Plans: Describing Uncertainty Scenarios and Reporting Their Dosimetric Consequences. Pract Radiat Oncol. 2018 Dec 15. pii: S1879-8500(18)30352-7.doi: 10.1016/j.prro.2018.12.002

**The assessments of localization, immobilization, tissue motion, and anatomical and physiological changes should be addressed explicitly in the protocol or within an appendix to the protocol.