

Guidelines for the Use of Proton Radiation Therapy in NCI-Sponsored Cooperative Group Clinical Trials

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The earlier proton radiation therapy (PRT) guidelines were created and communicated to all clinical trial groups by the National Cancer Institute (NCI) in 2007 and 2010. 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 on any facility that uses PRT to treat those patients participating in any applicable NCI-supported clinical trial. They are not to be construed as prescriptive of standards of care.

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 (http://www.qarc.org/benchmarks/Proton_Questionnaire.pdf)
- b. Annual monitoring of the proton beam calibrations by the Radiological Physics Center (RPC)
- c. Ability to electronically transfer treatment plans (<http://atc.wustl.edu/resources/index.html>)
- d. Successful irradiation of the RPC's baseline proton phantom(s)
- e. Successful completion of an on-site dosimetry review visit, to occur only after the center has been routinely treating patients for a minimum of 6 months and no fewer than 3 anatomical disease sites, and completion of the site visit report by the RPC recommending approval.

The RPC will coordinate the completion of the approval processes in conjunction with the other quality assurance offices.

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- and treatment technique-specific phantom irradiation
- b. Evidence that the institution has previously treated patients in the specific manner required by the protocol
- c. Clinical and technical rapid review of patient treatment plans for each patient enrolled
- d. Completion of a protocol specific knowledge assessment

e. Completion of a protocol specific electronic benchmark case

† Note: “Approval” as stated above refers to an institution’s “general” ability to use and deliver PRT, as evaluated by the RPC, for NCI funded clinical trials. Whereas, “credentialing” refers to the appropriate protocol QA center 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 RPC 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 (eg. 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. At this time, both scattered and scanned beam techniques may be used for cooperative group trials, but each technique used must be uniquely reviewed and approved by the RPC.

7. The IAEA TRS 398 protocol in conjunction with ICRU 78 recommendations are recommended for beam calibration and dose specification. In addition, it has been shown that the use of the ICRU 59 recommendations with N_x for beam calibration is equivalent to the IAEA TRS 398 (ICRU 78) protocol.

8. All proton doses shall be expressed as Relative Biological Effectiveness (RBE)-weighted absorbed dose, D_{RBE} (this quantity is equivalent to Cobalt-Gray-Equivalent (CGE)) employing a standard RBE of 1.1 with respect to ^{60}Co . The unit of RBE-weighted dose is gray (Gy(RBE)).

9. 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 RPC site visit or by remote review of the written procedures and records.

10. Doses will be specified to volumes using the standard nomenclature, i.e. GTV, CTV, and PTV as defined in ICRU Reports 50, 62, and 78. The GTV and CTV 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, lateral scatter, lateral penumbra, and distal penumbra. When a PTV is used to address the effects of uncertainties on the delivered dose distribution, ICRU 78 recommends that the PTV be defined relative to the CTV on the basis of lateral setup uncertainties and motion. Additional distal and proximal margins for each beam to take into account the uncertainties along the beam direction should assure the treatment of a consistent protocol-specified volume. The protocol should describe the rationale for the choice of uncertainties and mitigations for those uncertainties.

11. The protocol must provide a clear description of the dose prescription 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.

12. 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.*

13. Tissue volumes with a possibility of large motion require, especially so with scanned beams, 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 as part of protocol-specific credentialing.*

14. 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.*

*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.