

**ATC Guidelines for the Use of Proton Radiation Therapy in NCI Sponsored
Cooperative Group Clinical Trials
May 13, 2010**

Preamble:

The Advanced Technology Consortium (ATC) has facilitated the development of general guidelines for protocols that incorporate proton radiation therapy (PRT) as an option (http://atc.wustl.edu/credentialing/FINAL_PROTON_GUIDELINES_june_2007.pdf). The guidelines were previously communicated to all clinical trial groups by the National Cancer Institute (NCI), and this document (dated May 13, 2010) represents the latest version. There are potential advantages to patients from PRT but substantial concerns persist as protons are more sensitive than photons to uncertainties in the planning, optimization, and execution of radiation therapy. This reflects the nature of the interactions of protons with matter, and hence the need for credentialing and quality assurance procedures that are specific for PRT. The guidelines below are intended to ensure that when PRT is employed in the setting of a multi-institutional co-operative group clinical trial neither patient safety nor the study is compromised. The guidelines only specify the MINIMUM required of any facility that uses PRT to treat those patients participating in any NCI-supported clinical trial that requires or allows PRT. They are not to be construed as prescriptive of standards of care.

Guidelines:

1. Before treating any patients participating in a cooperative group protocol with proton radiation therapy (PRT), an institution must be appropriately credentialed for PRT by the QA Center or Cooperative Group designated in the protocol. Credentialing includes a successful site visit by the Radiological Physics Center (RPC), the ability to transfer treatment plans (digital data) to the designated QA Center, appropriate documentation of the institution's proton dosimetry system from dose to water through dose to the patient, and other protocol specific or QA Center requirements (see Addendum).
2. Both passive and scanned beams may be used, but the specific beam line delivery system (passive or scanned) must have been reviewed and credentialed by the RPC. Note, there are several different approaches used to implement proton scanning.
3. The IAEA TRS 398 protocol is recommended for beam calibration (see rationale 1), although ICRU 59 is acceptable. The RPC uses the IAEA protocol during its site visits.
4. All doses shall be expressed as RBE-weighted absorbed dose, D_{RBE} , employing a standard RBE of 1.1 with respect to Cobalt-60 (see rationale 2). The unit of RBE-weighted dose is gray (Gy).
5. Treatment planning shall be performed on a CT scan obtained with the patient in the treatment position. Correlation between the institutional CT treatment planning system "Hounsfield Units" (for the specific CT scanners and parameters) and "relative proton stopping power" must be established and documented at each institution. This will be reviewed during the RPC site visit (see rationale 3)

6. 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 identical for protons and photons. Every protocol that allows PRT must explicitly address issues unique to PRT in specifying the PTV, such as range uncertainties and lateral scatter. ICRU 78 recommends that the PTV be defined relative to the CTV on the basis of lateral uncertainties alone and that an adjustment is made within the beam-design algorithm to take into account the uncertainties along the beam direction. (see rationale 4)
7. In addition to the site visit, the RPC shall conduct annual remote monitoring of the proton calibrations relevant to clinical trials in which the facility is participating (see rationale 5).
8. Protocols permitting the use of proton therapy must clearly state the conditions under which proton therapy is allowed. Hence, protons may not be used to treat patients on protocols that do not specifically allow the use of protons.
9. Every protocol that allows PRT must specify a radiation oncologist and a physicist actively practicing at a proton facility, or explicitly identify QA Center designated individuals with proton expertise, who will be responsible for incorporating into that protocol (prior to submission to NCI) the appropriate dose terminology and specific constraints related to PTV and OAR, and associated QA listed in this guideline (see rationale 6).

Rationale:

1. The IAEA TRS-398 protocol is recommended by the ICRU 78 and is based upon a cobalt-60 dose-to-water calibration traceable to a national standard. The difference in calibration between the ICRU recommendations, ICRU 59, and the IAEA recommendations is quite small, less than 2%, though it depends upon the ion chamber used. There are published data on comparisons with proton calibrations using ICRU 59, which indicates good agreement among institutions.
2. The RBE and dose specification has been used historically by each of the facilities within the US, so this will allow for clinical continuity of treatment methods and results. ICRU 78 recommends the D_{RBE} nomenclature.
3. The conversion of HU to stopping power ratios determines the energy (range) required of the protons and must be performed at each institution. The HU to physical density calibration curve should be independently reviewed. Paragraph 6.4.6 of ICRU Report 78 is entitled "Compensation for heterogeneities" and describes two different methods for establishing the relationship between Hounsfield number and mass stopping power of protons, namely a direct-fit method and a stoichiometric method. Report 78 notes that typically the conversion from the Hounsfield number of water equivalent density leads to a 1 to 2 mm uncertainty in computing the effective range of a proton that penetrates approximately 10 cm into the patient. In addition, uncertainties in the CT measurements themselves can add an additional 1 to 2% uncertainty. Each participating institution is required to document their approach for establishing the

relationship between Hounsfield number and mass stopping power. The state of the art for soft tissue conversion of CT numbers to stopping powers is $\pm 3.5\%$.

4. ICRU 78 addresses proton specific issues regarding the PTV in paragraph 5.1.4.4. It recommends that “the PTV be defined relative to the CTV on the basis of lateral uncertainties alone.” It further recommends that “an adjustment must then be made within the beam-design algorithm to take into account the differences, if any, between the margins needed to account for uncertainties along the beam direction (i.e. range certainties) and those included in the so-defined PTV (i.e., based on lateral uncertainties).”

Thus, the PTV is the same for photon planning and for proton planning for the purposes of dose prescription and reporting. However, the PTV for protons accounts only for lateral uncertainties perpendicular to the beam direction. Proton planning requires an additional adjustment to take into account the margins needed to account for uncertainties along the beam direction, i.e. range uncertainties. Participating institutions must have a defined approach for addressing range uncertainties. The evaluation of a proton plan should be performed both on an individual beam basis to insure adequate proximal and distal coverage and on the summation of all beams to insure PTV coverage.

5. The RPC is funded by the NCI to maintain uniformity and NIST traceability of all physical dosimetry in NCI clinical trials, both photon and proton. The on-site visit will verify the proton beam calibrations and will capture the data needed by the QA center to:
 - a. Assess the accuracy and reproducibility of the CT HU to stopping power conversion
 - b. Assess the accuracy of the treatment planning algorithm
 - c. Assess the adequacy of patient specific immobilization techniques
 - d. Assess the in-room image guided patient positioning system(s)

Each of these factors will be evaluated in the context of specific protocol requirements. The exact details of the RPC visit will depend upon many factors, including the protocols on which the institution wishes to enter patients and the proton treatment delivery system. Repeat visits may be required.

In addition, the RPC will conduct annual reference dosimetry audits of each proton radiation therapy beam line previously credentialed.

6. The characteristics of protons are unique enough that they are not readily appreciated from the traditional photon experience. Hence, special knowledge and experience by the radiation oncologist and physicist is required in order to ensure patient safety and adequacy of the trial design. As with the early guidelines permitting the use of IMRT, protons can only be used on protocols that specifically allow the use of proton therapy.

Addendum:

Examples of other protocol specific or QA Center requirements for advanced technology modalities.

1. The protocol must explicitly address the localization and immobilization of both the patient and the tumor. There are several commercially available systems that can help achieve immobilization. The study chair and designated QA Center shall assess the adequacy of those systems for each individual protocol. For IMRT delivery, the residual motion after compensation techniques are applied should be explicitly specified in the protocol. The current literature indicates that with present-day techniques 5 mm of residual target motion is the smallest reasonable limit for intra-thoracic anatomical structures.
2. The protocol should describe the rationale for the choice of margins (IM and SM) to be used for expanding CTV to PTV.
3. The protocol must require that the effects of tissue heterogeneities be included in the dose calculations for plan evaluation, dose prescription and MU calculations.
4. The protocol must provide a clear description of the prescription dose as well as dose heterogeneity permitted in the PTV. The protocol must also specify the volume to be covered by the prescription dose (for example, the 60 Gy isodose must cover 95% of the PTV).
5. The protocol must clearly specify the organs at risk (OARS) and/or the planning organ-at-risk volumes (PRVs) and include guidelines for contouring each OAR/PRV. Dose constraints for each OAR/PRV must also be specified.
6. The GTV, CTV, PTV, and OAR/PRV must be delineated on each slice of the 3-D volumetric imaging study in which that structure exists.
7. The protocol must specify the procedures that should be in place for documenting correct, reproducible positioning of patient and target.
8. The treatment machine monitor units (MUs) generated by the PRT planning system must be independently checked prior to the patient's first treatment. Patient specific quality assurance measurements can suffice as an independent check. The protocol should specify criteria for acceptance of these measurements.