Department of Health & Human Services   Public Health Service

Walter J. Curran, Jr., M.D., Chairman   July 17, 2002
Radiation Therapy Oncology Group
1101 Market Street, 14th Floor
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Dear Dr. Curran:

The NCI Cancer Therapy Evaluation Program has received numerous requests to permit utilization of IMRT techniques as a routine option into clinical trials protocols that utilize radiation therapy. This document is to serve as a template for development of protocols that wish to incorporate IMRT as a routine radiation therapy treatment technique.

Radiation therapy treatment planning and delivery are in the process of changing dramatically. This change is being driven in large part by continuing advances in computer technology that has led to the development of sophisticated three-dimensional radiation treatment planning (3DRTP) systems and computer-controlled radiation therapy treatment delivery systems. Such planning and delivery systems have made practical the implementation of three-dimensional conformal radiation therapy (3DCRT). The goal of 3DCRT is to conform the spatial distribution of the prescribed dose to the 3D target volume (cancerous cells plus a margin for spatial uncertainties), while at the same time minimizing the dose to the surrounding normal structures. The delivery of 3DCRT is typically accomplished with a set of fixed radiation beams, which are shaped using the projection of the target volume. The radiation beams normally have a uniform intensity across the field, or, where appropriate, have this intensity modified by simple beam fluence modifying devices like wedges or compensating filters.

Now, even before this form of radiation therapy has been implemented throughout the radiation oncology community, a newer type of conformal planning and delivery technology called intensity modulated radiation therapy (IMRT) is rapidly evolving. IMRT treatment plans are often generated using 3DRTP systems, which use automated computer optimization techniques (sometimes referred to as inverse planning) to determine the distribution of optimized non-uniform radiation beam intensities across the target volume. It is important to fully appreciate that modern IMRT techniques are significantly more complex than traditional forms of radiation treatment, including conventional 3DCRT. In addition, a precise definition of just what constitutes an IMRT plan is still evolving as the technology develops. It clearly is much more than just the use of non-uniform beam intensities. Beam modifiers, such as wedges and compensators, have been used for many years to compensate for missing tissue, and in some instances to shape dose distributions. The American Medical Association's latest Current Procedural Terminology (CPT 2002) manual defines IMRT as a dose plan that is optimized using inverse or forward planning techniques for modulated beam delivery (e.g., using a binary collimator such as the Nomos MIMiC collimator, or with a dynamic conventional multileaf collimator (MLC) system) to create a highly conformal dose distribution. Their definition also clearly states that the plan must include dose-volume histogram (DVH) analysis for target and critical structure partial tolerance specifications, and that the computer plan dose distribution must be verified for positional accuracy based on dosimetric verification of the intensity map, along with verification of treatment set up, and interpretation of the verification methodology.

Currently, most published reports on the clinical use of IMRT are either treatment planning studies showing the improvement in dose distributions generated by IMRT and involve only a limited

number of cases, or dosimetric studies confirming IMRT treatment. There are no published reports, at present, of prospective randomized clinical studies involving IMRT, and this lack of information clearly limits our knowledge of how clinical outcomes will be affected by the use of IMRT. It is clear that IMRT offers the opportunity of more conformal dose distributions and for increasing daily treatment fraction to tumor with a decreased dose to normal tissues. Although most agree with these potential advantages in physical dose distribution with IMRT, and therefore the potential for improvement in patient outcomes, there exists concern for actual IMRT treatment execution, including proper plan optimization, as optimization algorithms and quality assurance (QA) procedures for this new modality are still evolving. Specific concerns include the potential to miss the tumor (or at least underdose a portion of the tumor) and/or to have significant high dose volumes in the normal tissues. There is also the additional concern that the wide spread use of IMRT could lead to an increased incidence of radiation induced carcinomas due to the larger volume of normal tissue exposed to lower doses and the increase in whole body doses as a result of the increased monitor units required for the delivery of IMRT. This may be especially important in the pediatric and young adult patient populations.

The problem of specifying and planning the dose distribution to a high dose target volume and a lower dose to a clinical target volume with little or no regard to an accounting for geometric uncertainties is present with IMRT. In such situations, the physician is evaluating a dose distribution to a patient image that can be substantially different from what is actually delivered. The reality is that over the course of treatment the patient's target volume is going to vary from the geometry captured at the initial imaging study for treatment planning due to organ movements and daily patient setup variations, as well as changes in the tumor volume over the course of the radiation therapy. In addition, one must fully appreciate that IMRT, depending on how it is implemented, can be "less forgiving" than conventional radiation therapy in regard to the effects resulting from geometric uncertainties. For example, IMRT dose distributions are shaped to conform more closely to the tumor volume and avoid normal tissues, introducing large gradients near the perimeter of both the target volume and normal structures. Also, because IMRT techniques (unlike 3DCRT) treat only a portion of the target volume at a particular time, there is the potential for significant dosimetric consequences if the patient and/or the target volume move during treatment (intrafraction geometric uncertainties). For example, respiratory related excursions of a target volume could potentially cause the tumor to be grossly underdosed despite a beautiful dose distribution in a static plan. Furthermore, since IMRT treatments typically take longer than conventional radiation therapy treatments, the patient must remain in a fixed position for a longer period of time, increasing the vulnerability to intrafraction geometric uncertainties. Hence, it is clear that IMRT imposes a more stringent requirement than conventional radiation therapy on an accounting for both intrafraction and interfraction patient position and organ motion.

In 1999, the NCI funded the Advanced Technology Radiation Therapy Quality Assurance Review Consortium (ATC), which is composed of the ITC, QARC, Radiological Physics Center (RPC), and RCET. This QA consortium represents the QA review process for radiation therapy for most if not all of the cooperative clinical groups. This QA consortium will provide a unique opportunity to further develop guidelines for the utilization of IMRT treatment techniques in protocols that will be transparent to all of the cooperative groups.

In summary, it is apparent that comprehensive QA is vital for IMRT due to the high dose gradients and non-intuitive nature of the treatment planning. It is not guaranteed that all institutions that may wish to use IMRT in a routine clinical trial perform adequate quality assurance. This is a special concern for facilities that lie outside the orbit of cooperative groups but that may enter patients through the CTSU.

The NCI held a meeting of the radiation oncology committee chairs from the NCI funded clinical trials groups on June 20, 2002. The following guidelines were discussed and agreed upon. These guidelines are meant only for clinical trials in which the utility of IMRT is not the purpose of the study, but where radiation therapy is part of the study. This does not mandate that any specific protocol allow IMRT, but if it is to be allowed the following requirements must be submitted as part of the initial protocol or as an amendment if IMRT is to be subsequently allowed.

Protocol Requirements

1. Protocols permitting IMRT treatment delivery must be written using the nomenclature defined in the NCI IMRT Working Group Report5 (IMRT Collaborative Working Group: Intensity modulated radiation therapy: current status and issues of interest. Int. J. Radiat. Oncol. Biol. Phys. 51:880-914, 2001) and the International Commission on Radiation Units and Measurements (ICRU) Reports 50 and 62 for specifying the volumes of known tumor, i.e., Gross Tumor Volume (GTV), the volumes of suspected microscopic spread, i.e., Clinical Target Volume (CTV), and the marginal volumes necessary to account for setup variations and organ and patient motion, i.e., Planning Target Volume (PTV). Report 62 introduced the concept of the Planning Organ at Risk Volume (PRV), in which a margin is added around the critical structure to compensate for that organ's geometric uncertainties. The PRV margin around the critical structure is analogous to the PTV margin around the CTV. The use of PRV concept is even more important for those cases involving IMRT because of the increased sensitivity of this type treatment to geometric uncertainties. The PTV and the PRV may overlap, and often do so, which implies searching for a compromise in weighting the importance of each in the planning process.
2. The protocol must provide a clear definition of the Gross Tumor Volume (GTV), Clinical Target Volume, and Planning Target Volume (PTV).
3. The protocol must provide a clear definition of the prescription dose and dose heterogeneity allowed throughout the PTV. Heterogeneity must be compatible with the requirements for non-IMRT treated patients.
4. The protocol must require that a volumetric treatment planning CT study be used to define the GTV.
5. The protocol must clearly define the organs-at-risk that are required for each study and provide clear guidelines for contouring each organ-at-risk defined in the study. Dose constraints for each organ-at-risk in the irradiated volume must be defined. This should include a reasonable definition of major and minor deviation for each item of interest. Participants are required to be within the protocol specified limits.
6. The GTV, CTV, PTV, PRV(s), and skin contours must be depicted on all planning CT slices in which each structure exists.
7. The protocol must require that specific procedures be in place to insure correct, reproducible positioning of the patient. As a minimum, orthogonal (AP and lateral) DRRs and corresponding orthogonal portal images (film or electronic) are to be required.
8. Copies of all images required by the protocol in defining the GTV must be submitted to the cooperative group QA office for review. The intended dose distribution from the planning system in the coronal, axial, and sagittal planes must be submitted for QA review. Isodose lines superimposed on CT images must be clear and comprehensive. Areas receiving more than 100% of the prescription dose must be clearly indicated, as well as "cold spots" within the PTV. DVHs for the GTV, CTV, PTV, and all PRVs defined for the study must be submitted for QA review. Review must be completed within the first week of treatment or before the treatment is 15% completed.

9. A DVH will be submitted for a category of tissue called "unspecified tissue" that is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. This will help insure that the IMRT plan does not result in increased doses in normal tissues that were not selected for DVH analysis. This must also be reviewed within the first week of treatment or before the treatment is 15% completed.
10. The treatment machine monitor units generated using the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry.
11. IMRT for lung cancer, esophageal tumors, or other areas with significant volumes of air, or where tumor mobility cannot be easily accounted for is not allowed.

Credentialing

As a minimum, the IMRT questionnaire and benchmark developed by the ATC must be completed by each institution, and reviewed and approved the cooperative group's QA The institution can then be approved for treatment with IMRT on study. The ATC IMRT questionnaire and benchmark case is attached. Based on feedback from cooperative groups, the ATC will continue to refine the IMRT benchmark and promote it as a credentialing document that will be recognized by all groups, at least for one tier of credentialing.

In addition, some cooperative groups may wish to require that a phantom be planned and irradiated using IMRT as a part of the IMRT credentialing requirement for specific protocols In such cases, the RPC has developed anthropomorphic and geometric phantoms to meet the specific requirements of the protocol. If future protocols in which IMRT plays a significant role require this additional credentialing, the ATC will develop site-specific phantoms similar to that used for RTOG H-0022. The phantoms will contain imageable objects definable as the target, appropriate critical structures, heterogeneities, and dosimeters. The phantoms are relatively inexpensive and can be commissioned quickly by the RPC . These phantoms are intended to allow quantitative assessment of the institution's ability to localize the target, plan a treatment, and deliver a dose distribution specified by the protocol. The phantoms will be designed to assess the accuracy of a delivered dose (+5%) near the center of the target, the dose homogeneity (if appropriate) across the target, and the positioning of the field relative to the target (±2mm). The phantoms will be constructed and mailed to the participating institutions. Experience suggests that the turnaround time for a phantom sent to an institution is one to two months, depending on the complexity of the treatment.

Thank you for your cooperation in this matter. The NCI sponsored ATC is available to assist your group in meeting any or all of these requirements. The websites of the ATC members are attached.

Sincerely,

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