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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

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Dear Group Chair/Administrator:

It has been a little over 3 years since the NCI convened a group of experts to address the issue of using Intensity Modulated Radiation Therapy (IMRT) in clinical trials. At that time it was decided that there was need for certain guidelines to ensure the safety and comparability of the radiation treatments (see IMRT Guidelines 2002 at http://www3.cancer.gov/rrp/). The purpose of this letter is to announce revisions to those guidelines that recognize the advances in the technological capabilities as well as in the clinical utility of this treatment option.

Although most agree that there are potential advantages in the physical dose distributions attainable with IMRT, and therefore potential improvements in patient outcomes, there still exists concern for actual IMRT treatment execution, including proper plan optimization. Thus there remains a need for credentialing and quality assurance procedures that are unique to the IMRT process.

While these revised guidelines reiterate the previous requirements for a multi-element quality assurance program they now: a) emphasize the need for volumetric imaging [guideline 1] in the proper implementation of IMRT, b) require the use of heterogeneity – corrected dose distributions [guideline 4] and c) they now allow for the use of IMRT for intra-thoracic tumors with appropriate corrections for the lung heterogeneity and target motion [guideline 12]. Thus they represent an expansion in the possible use of IMRT in clinical trials.

We ask that you ensure that these guidelines are distributed throughout the **RPC** Clinical Trials Group, and its affiliated members, and especially to your Radiation Oncology Committee so that we may expedite their implementation within CTEP review. If you have any questions or need follow-up please contact:

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Sincerely,

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Enclosures:
IMRT NCI Guideline

The National Cancer Institute Guidelines for the Use of Intensity-Modulated Radiation Therapy in Clinical Trials

Preamble

Intensity-modulated radiation therapy (IMRT) represents a new paradigm in radiation therapy that requires knowledge of patient immobilization, multimodality imaging, setup uncertainties and internal organ motion, tumor control probabilities, normal tissue complication probabilities, three-dimensional (3-D) dose calculation and optimization, and dynamic beam delivery of non-uniform beam intensities. This new process of planning and treatment delivery shows significant potential for further improving the therapeutic ratio and reducing toxicity. Therefore, there is a great push to make this technology available for patients enrolled in clinical trials. Many of the IMRT applications reported in the recent literature were developed by academic institutions and tailored to their own local environment. These institutions expended significant resources learning the nuances of this technology. It is unrealistic to expect the majority of clinics to go through the same process. However, there is enough published literature concerning the clinical use of IMRT at this point, that it is now possible to provide more comprehensive recommendations for clinical trial groups on the use of IMRT in protocols.

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program receives numerous requests to permit utilization of IMRT techniques as a routine option in clinical trial protocols that utilize radiation therapy. This document serves as a template for development of protocols that wish to incorporate IMRT as a radiation therapy treatment technique option.

Current Status of IMRT and Its Use In Clinical Trials

IMRT is still a nascent technology. It allows the clinical implementation of highly conformal, even non-convex, dose distributions. Traditional radiation therapy techniques, including three-dimensional conformal radiation therapy (3DCRT) with uniform radiation intensity and/or with simple beam fluence modifying devices like wedges, do not provide a method for sparing critical structures that push into and are partially or fully surrounded by a target or combination of targets. True three-dimensionally conformal dose distributions are now possible in large part by continuing advances in computer technology that has led to the development of sophisticated three-dimensional radiation treatment planning (3DRTP) systems with inverse planning capabilities and computer-controlled radiation therapy treatment delivery systems equipped with a multileaf collimator (MLC). Such planning and delivery systems have made practical the implementation of 3DCRT with modulated radiation fluence. The ultimate goal of 3DCRT is to conform the spatial distribution of the prescribed dose to the 3-D target volume (cancerous cells plus a margin for spatial uncertainties), while at the same time minimizing the dose to the surrounding normal structures.

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. We define IMRT for the purpose of this document as a dose plan and treatment delivery that is optimized using inverse or forward planning techniques for modulated beam delivery, using either a binary collimator, or with a conventional MLC system using either “sliding window” (DMLC) or “step and shoot” (SMLC) modes; note, this definition also includes techniques with compensators designed by

inverse planning techniques, to create a highly conformal dose distribution. The IMRT plan includes dose planning objectives and constraints, criteria for target and critical structure expansions, 3-D dose distributions, DVH analysis for targets and critical structures, and plan verification.

It is important to fully appreciate that IMRT techniques present a set of challenges that are significantly more complex than traditional forms of radiation treatment. These include the following:

- IMRT requires a detailed understanding of radiographic anatomy as well as other developing 3- and 4-D representations of the patient in order to correctly delineate both tumor/target volume(s) and organs at risk (critical structures). With IMRT using inverse planning, the target must be outlined precisely or it might not be treated to the prescribed dose. More importantly, if a critical structure is not outlined, it might not be not spared.
- The conformal dose distribution and high dose gradients in IMRT mandate improved patient immobilization as well as quantitative assessment of target and organ motion detection and control.
- IMRT dose distributions are often more inhomogeneous within the target than traditional conformal therapy. In general, dose inhomogeneity increases as the required dose gradient between the target and an adjacent critical structure increases, the concavity of the required dose distribution increases, the distance between the target and a critical structure decreases, and the number of available beam directions decreases. Under these conditions, prescribing the dose to a single point becomes unacceptable.
- IMRT doses are often calculated by dividing beams into smaller sections, called *beamlets,* which have varying intensities. Therefore, the mechanical accuracy of the

IMRT delivery system and accurate modeling of machine parameters such as head scatter, penumbra, and transmission becomes very important. Also these (often small) beamlets can be much more problematic for dose computation algorithms. Their impact on the resultant dose distribution may not be obvious, and thus additional patient specific quality assurance tests are required.

- Accounting for heterogeneities is more important for IMRT because they can affect some beamlets more than others, giving rise to localized dose distribution differences that may be significant.
- IMRT plan evaluation requires more diligence than does traditional 3DCRT planning. IMRT can create cold spots or hot spots in unexpected locations, which are not easily appreciated on dose volume histograms (DVHs). IMRT plan evaluation requires inspection of isodose distributions on each image slice.
- Respiratory motion can cause far more problems for IMRT treatments than for traditional treatments. The effect of breathing and other movements on the summation of beamlets with different intensities on a static image can be significant. Care must be taken in the acquisition of the CT dataset used in the planning process to avoid motion artifacts while being representative of the average location of the anatomy. As with traditional treatments, the mapping of isocenter coordinates to the patient must consider the part of the breathing cycle imaged on the data set.
- Target volumes located near the skin surface may pose problems with the inverse optimization process that must be avoided.
- The expansion of target contours in three dimensions to account for uncertainties in planning and delivery may result in the intersection of two structures and thereby create

problems in inverse planning optimization. Expansion into air or into the buildup region may also cause problems (see above).

- IMRT plans that allow simultaneous treatment of gross and subclinical disease at different doses per fraction can have radiobiological consequences that differ from those of traditional plans delivered with a uniform dose per fraction. The longer treatment times typical of some IMRT treatments may also be radiobiologically relevant.
- IMRT can result in a higher whole-body dose due to leakage radiation because IMRT plans often require substantially more monitor units (MU) to deliver the prescribed dose.

Currently, most published reports on the clinical use of IMRT are single institution studies, and are either treatment planning studies for a limited number of cases showing the improvement in dose distributions generated by IMRT, 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 the effect of the use of IMRT on clinical outcomes. It is clear that IMRT offers the opportunity of more conformal dose distributions and for increasing the daily treatment fraction to the target volume 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 therapy associated carcinomas due to the larger volume of normal tissue

exposed to low doses and the increase in whole body doses as a result of the increased MU required for the delivery of IMRT. This may be especially important in the pediatric and young adult patient populations.

Specifying and planning a dose distribution that provides a high dose to the target volume and a lower dose to organs at risk requires a careful accounting for geometric uncertainties when IMRT is used. The reality is that over the course of treatment, the patient's target volume will 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 possible changes in both the patient's physical dimensions and the tumor volume over the course of the radiation therapy. In such situations, the physician must evaluate a computed dose distribution to a patient image that can be substantially different from the dose distribution actually delivered. 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 (known as intrafraction geometric uncertainties). For example, respiratory-related excursions of a target volume could potentially cause the tumor to be grossly under-dosed despite an apparently satisfactory 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 requiring an accounting for both intrafraction and interfraction patient position variations and organ motion.

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.

These guidelines were developed for the utilization of IMRT treatment techniques in protocols with the goal that they be clear enough to be consistently applied within all of the cooperative groups. They are meant to serve only as minimal standards for NCI-supported clinical trials in which IMRT is employed. They do not mandate that any specific protocol allow IMRT, but if IMRT is to be allowed the following requirements must be included as part of the initial protocol or as an amendment if IMRT is to be subsequently allowed.

Protocol Requirements

1. The protocol must require that a 3-D treatment planning volumetric imaging study be used to define the target volumes and critical structures.

2. Protocols permitting IMRT treatment delivery must be written using the nomenclature defined in the NCI IMRT Working Group Report (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). The CTV is potentially affected by large physiological movements, which should be explicitly accounted for with an internal margin (IM). The IM should compensate for variation in size, shape, and position of the CTV during treatment in relation to an internal reference point. Thus PTV for a mobile target represents a volume that encompasses the CTV, a set-up margin (SM) that specifically accounts for spatial uncertainties in patient positioning and treatment delivery, and an IM for the residual internal organ motion[1]. ICRU Report 62 introduced the concept of the planning organ at risk volume (PRV), in which a margin is added around the organ at risk (OAR) to compensate for that organ's geometric uncertainties. The PRV margin around the critical structure that must be spared 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

[1] ICRU Report 62 refines this definition of planning target volume by introducing the concept of an Internal Margin (IM) to take into account variations in size, shape, and position of the CTV in reference to the patient's coordinate system using anatomical reference points, and the concept of a Set-up Margin (SM) to take into account all uncertainties in patient beam positioning in reference to the treatment machine coordinate system. Report 62 defines the volume formed by the CTV and the IM as the Internal Target Volume (ITV). The ITV represents the movements of the CTV referenced to the patient coordinate system and is specified in relation to internal and external reference points, which preferably should be rigidly related to each other through bony structures. The ITV concept is likely to be used mostly by researchers studying internal organ motion. Note however, that the introduction of the ITV concept does not change the global concept and definition of the PTV as a means of accounting for geometric uncertainty. In most cases, the practicing physician can skip having to explicitly define the ITV. However, how the IM and SM should be combined is not at all clear. Simple linear addition of the two margins will generally lead to an excessively large PTV that would exceed patient tolerance and not reflect the actual clinical consequences. Thus, the risk of missing part of the CTV must be balanced against the risk of complications due to making the PTV too large. ICRU states that a quadratic approach similar to that recommended by the Bureau International des Poids et Mesures can be used.

may overlap, and often do so, in which case a compromise must be found when weighing the importance of each in the planning process.

3. The protocol must provide a rationale for the choice of margins (IM and SM) to be used by the participating institutions to expand CTV to PTV.
4. The protocol must require that a heterogeneity-corrected dose distribution be prepared for plan evaluation and dose prescription.
5. The protocol must provide a clear definition of the prescription dose and dose heterogeneity allowed throughout the PTV. Dose heterogeneity for IMRT patients must be similar to the requirements for non-IMRT treated patients treated on the same protocol.
6. The protocol must clearly define the OARs and/or PRVs that are required for each study and provide clear guidelines for contouring each OAR/PRV defined in the study. Dose constraints for each OAR/PRV in the irradiated volume must be defined. Participants are required to be within the protocol specified limits.
7. The GTV, CTV, PTV, OAR (s), PRV(s), and skin contours must be depicted on all slices of the 3-D volumetric imaging study in which each structure exists.
8. The protocol must require that specific procedures be in place to insure correct, reproducible positioning of the patient. At a minimum, orthogonal (AP and lateral) digitally reconstructed radiographs (DRRs) and corresponding orthogonal weekly portal images (film or electronic) are to be required.
9. Copies of all images required by the protocol in defining the GTV must be submitted to the cooperative group QA office for possible review. The intended dose distribution computed by the planning system in the coronal, axial, and sagittal planes must be submitted for QA review. Isodose lines superimposed on representative slices of the 3-D volumetric imaging

study 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.

10. A DVH will be submitted for a category of tissue called “non delineated 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 ensure that the IMRT plan does not result in increased doses in normal tissues that were not selected for DVH analysis.
11. The treatment machine MU 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.
12. The use of IMRT for intra-thoracic treatments, in which significant heterogeneities are encountered and tumor mobility is likely, is permitted ONLY when correction for heterogeneities and accounting for target motion are addressed satisfactorily in the design of the protocol.
13. Before participating in a cooperative group trial involving IMRT, an institution must be credentialed, as described below.
14. Finally, it is strongly recommended that the data from these treatments be archived at either a central QA facility or at the home institution so that they may be made available for later analysis, due to the emergent nature of these IMRT procedures.

Credentialing

In recognition of the added complexity of IMRT and other emerging technologies in radiation oncology, the NCI funded the Advanced Technology Consortium (ATC), which is composed of the Image-Guided Radiation Therapy Center (ITC), the Quality Assurance Review Center

(QARC), the Radiation Therapy Oncology Group (RTOG) QA Center, the Radiological Physics Center (RPC), and the Resource Center for Emerging Technologies (RCET). The ATC is responsible for building an infrastructure to support the QA review process for advanced technology radiation therapy trials for most of the clinical cooperative groups. Credentialing is an important part of that QA process and one pathway for credentialing is the IMRT questionnaire and benchmark developed by QARC and adopted by the ATC (*Int J Radiat Oncol Biol Phys. 59 (2004): 1257-1262*). Satisfactory completion of the benchmark and its approval by the cooperative group's QA process credentials the institution for treatment with IMRT on one or more clinical trials, as determined by the cooperative group. The IMRT benchmark is intended to be completed by an institution with no more effort than that required for a typical IMRT patient. Its goal is to evaluate the ability of a treatment planner to understand and meet treatment planning goals and OAR dose constraints while testing the capabilities of the institution's IMRT treatment planning system. It also requires the institution to demonstrate their QA procedures and provide verification of agreement of calculated and delivered dose. If an institution has already successfully completed the questionnaire and benchmark for one study, it will suffice for other group studies unless the specific protocol requires additional data.

Some cooperative groups may wish to require that an anthropomorphic phantom be planned and irradiated using IMRT. This in fact has been the case for the RTOG. For this purpose, the RPC has developed a family of anthropomorphic phantoms that meet the requirements of current protocols. Each phantom can be mailed to an institution, which will acquire a CT scan of the phantom, develop a treatment plan, and deliver the treatment to the phantom before shipping it back to the RPC for analysis. The phantoms contain imageable objects definable as the target, appropriate organs at risk, and heterogeneities, and also contain suitable dosimeters. These

phantoms allow quantitative assessment of the institution's ability to localize the target, plan a treatment, and deliver a dose distribution specified by the protocol. Appropriate criteria for agreement between the treatment and the isodose plan will be agreed upon between the RPC and the study group.