



Summary of CTAF Roundtable on Intensity Modulated Radiation Therapy (IMRT) for Prostate Cancer

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Background

On February 12th, 2007, the California Technology Assessment Forum (CTAF) convened a “IMRT Roundtable on Prostate Cancer” to discuss issues surrounding the role and evidence base of IMRT as a treatment for prostate cancer. IMRT for prostate cancer was an agenda item at two prior CTAF meetings where discussion focused on a technology assessment that concluded IMRT for prostate cancer was investigational. The investigational status was based on the lack of evidence from controlled trials proving that IMRT provided any incremental benefit over the conventional 3D conformal radiation therapy (3D-CRT). However, advocates of IMRT pointed out that IMRT should not be considered a new form of radiation therapy subject to distinct technology assessment. Furthermore, advocates pointed out that dose planning studies of IMRT documenting reduced radiation to normal tissues were an acceptable surrogate outcome. In 2005, the CTAF tabled the issue for further study. The 2007 IMRT Roundtable on Prostate Cancer was designed to provide a forum for a more thorough dialog among a variety of stakeholders. Meeting attendees included representatives from CTAF, the Blue Shield of California Foundation, Blue Shield of California, the National Cancer Institute, American Society of Therapeutic Radiology and Oncology (ASTRO), the American College of Radiology, the National Cancer Institute (NCI), the Center for Medical and Technology Policy, practicing radiologists and a patient advocate.

A background paper, titled “Intensity Modulated Radiation Therapy: Next Generation 3-D CRT or Distinct Form of RT ” was prepared and distributed before the meeting to provide an initial framework for discussion. This paper reviewed the characteristics of IMRT to clarify whether or not this technology was considered a unique type of radiation delivery, or represented an evolution of existing radiation therapy techniques. In addition, the paper reviewed the literature regarding IMRT and prostate cancer. Specific gaps in the literature were recognized. Finally, there were formal presentations from ASTRO and from Dr. Bhadrasain Vikram, representing the NCI, who summarized the deliberations of the December 2006 NCI Workshop on Advanced Technologies in Radiation Oncology.

Discussion at the IMRT Roundtable was centered on the following interrelated topics:

- Is IMRT a distinct modality of radiation therapy compared to 3D-CRT?
- Are dose planning studies an adequate surrogate outcome validating the incremental value of IMRT in reducing toxicity?
- Are randomized trials comparing IMRT to 3D-CRT either ethical or feasible? If not, what kind of data is available, or can be collected?

The following summarizes the debate around these three issues.

Is IMRT a distinct modality of radiation therapy compared to 3D-CRT?

The background paper summarized the multiple steps that are inherent in IMRT. This component of the paper was based in part on a guidance document issued by the NCI describing the use of IMRT in clinical trials. This NCI guidance document pointed out that the dose distributions of IMRT are highly complex, potentially leading to unforeseen complications and that IMRT may involve altered time-dose fractionation and dose heterogeneity for both the target and normal tissues compared to 3D-CRT. Additionally, the more precisely a tumor is targeted, the less error is allowed in patient set-up and treatment planning, i.e. there is a higher risk that an inappropriately high dose will be delivered to normal tissues, and an inappropriately low dose to the target lesion. This latter point was echoed by Dr. Vikram who emphasized the importance of quality assurance (QA) to ensure the potential benefits of IMRT. As an example, Dr. Vikram summarized the experience of the NCI who set up a rigorous QA program for institutions participating in NCI sponsored trials involving IMRT. This QA program was based on phantoms to verify the IMRT treatment plan. A significant minority of these institutions, which primarily represented academic and research institutions, failed the QA standards. This data was collected beginning in 2000, and experience with IMRT has grown exponentially since then. However, the significant QA demands of IMRT create concerns for less experienced institutions.

Advocates of IMRT pointed out that it is extremely difficult to delineate between 3D-CRT and IMRT and the term IMRT may be used in different ways by different people. Essentially, IMRT is the result of an ongoing stepwise evolution of the many individual components of 3D-CRT. Similar to other medical technologies, many steps of the evolution are related to computer programming. The incremental value of computer programming on an existing technology, such as radiation therapy, has generally not been subjected to a distinct technology assessment and medical policy development. It should also be noted that currently the QA requirements are more stringent for IMRT compared to 3D-CRT. For example, for reimbursement for IMRT, the Centers for Medicaid and Medicare Services (CMS) requires QA using a phantom. In contrast, phantoms are rarely used for 3D-CRT. Therefore, at the present time, IMRT is held to a higher standard compared to 3D-CRT.

Are dose planning studies an adequate surrogate outcome validating the incremental value of IMRT in reducing toxicity?

It is well established that the risk of normal tissue complications is a function of the radiation dose delivered to normal tissue and the volume of normal tissue irradiated. Additionally, there was general consensus that dose planning studies document that normal tissues, such as the bladder and rectum, can be spared using IMRT techniques. However, there was considerable debate whether clinical studies were required to verify these predicted outcomes. Advocates of IMRT pointed out that several randomized controlled trials of 3D-CRT compared to 2D radiation therapy verified that the predicted reduction in toxicities based on planning studies was observed in the clinical studies. Considering that IMRT represented a step-wise evolution of 3D-CRT, this proof of principle could be extrapolated to IMRT.

In contrast, other Roundtable participants pointed out that there are many examples of randomized controlled studies that surprisingly showed no effect of technologies that were widely thought to be beneficial based on pathobiologic principles. Cited examples included autologous bone marrow transplantation (ABMT) for breast cancer (where initial studies had suggested that dose escalation could improve survival rate), lung volume reduction surgery for emphysema (where removal of over expanded lung was thought to improve ventilation) and anti-arrhythmic therapy for patients with recent myocardial infarctions (where it was thought that eliminating arrhythmias would improve survival). Many advocates of these therapies were firmly convinced of their efficacy and resisted randomized studies. In all of these cases, results of the randomized studies showed no effect, and in some cases there was an increased mortality. Advocates of IMRT pointed out that these studies were not analogous to IMRT for the prostate, where IMRT was not designed to improve the survival, but primarily to reduce side effects. Specifically, IMRT was entirely consistent with well-known radiobiologic principles guiding treatment planning, i.e. creating greater conformal doses to the target volume while sparing organs at risk.

Are randomized trials comparing IMRT to 3D-CRT either ethical or feasible? If not, what kind of data is available, or can be collected?

A number of barriers to conducting randomized studies comparing IMRT and 3D-CRT in prostate cancer were identified as follows:

- If one accepted that dose planning studies were an accepted surrogate outcome a comparative trial would be considered questionably ethical. Essentially, a radiation oncologist would have to encourage a patient to be randomized, while knowing that a patient randomized to 3D-CRT would receive higher doses to organs at risk, with a predictable increase in toxicities.
- Patients are well educated and will specifically request IMRT, and thus are unlikely to agree to randomization.

- IMRT is widely diffused and is now accepted as a standard therapy. Ongoing randomized trials are studying other aspects of radiation therapy, such as dose escalation with either 3D-CRT or IMRT. While the results will be stratified according to the type of radiation therapy the patient received, it is unlikely that there will be enough patients in the 3D-CRT group to permit robust comparisons.
- Randomized trials in radiation oncology have focused on issues of radiobiology, patient selection criteria, and dose escalation. IMRT at standard doses does not fit any of these parameters.
- Any randomized trial of prostate cancer therapy is difficult due to the prolonged natural history of prostate cancer. Radiation therapy for prostate cancer will likely to continue to evolve during the long follow up period required.
- The NCI is unlikely to fund clinical trials comparing 3D-CRT to IMRT, which would primarily address toxicity issues. NCI will likely assign a higher priority to trials addressing novel therapies for malignancies with few treatment alternatives.
- The lack of payor support for clinical trials creates additional barriers.

Given these barriers, discussion focused on other data and trial designs. Data on acute toxicity is beginning to emerge from large case series from single institutions. This data can be compared to historical and contemporaneous data on 3D-CRT. Data on long term complications, such as urinary complications which can evolve over many years, will be harder to assess. There are also concerns regarding the risk of secondary malignancies associated with IMRT, based on both the treatment time and the increased low dose exposure to surrounding tissues. Given the low incidence of a secondary malignancy, its assessment is extremely difficult if not impossible, particularly given the average age of patients with prostate cancer treated with IMRT.

Sean Tunis, MD, provided an introduction to the Center for Medical Technology Policy (CMTP) a private, non-profit organization that provides a neutral forum in which patients, clinicians, payers, manufacturers and researchers can work together to design and implement prospective, real world studies to inform health care decisions. The CMTP recognizes that payors and providers share the same agenda to gather more data to enable more informed decision making by patients. Payors can facilitate gathering this data by participating in a variety of trial designs. One model is the CMS program of “coverage with evidence development” where participation in a trial or registry is a condition of coverage eligibility. The CMTP is currently considering five potential pilot project topics, including IMRT. Small multi-disciplinary workgroups, consisting of product developers, clinicians, payers, methodologists, patients and other stakeholders, have now been formed for each potential topic. The role of these workgroups is to:

- Identify the specific questions that health care decision makers have about each technology
- Determine the study methods that will be needed to address these questions, with emphasis on real-world, pragmatic designs
- Develop study protocol outlines
- Initiate partnerships necessary for study funding and implementation

Summary

At the end of the IMRT Roundtable meeting, there was still a divergence of opinion regarding whether IMRT represented a distinct type of radiation therapy subject to a distinct technology assessment. Advocates of IMRT felt that this technology represented one indistinct step in the ongoing evolution of radiation therapy, while representatives of the payor community pointed to the differences outlined by the NCI Guidance document for IMRT and suggested that clinical trials are warranted. However, there was a general consensus that randomized trials comparing the two technologies are probably not feasible, given the rapid diffusion of IMRT and its emergence as the standard of care. Other data and trial designs were discussed. Data on acute toxicities that is beginning to emerge from large case series can be compared indirectly to historical and contemporaneous data on 3D-CRT. The Center for Medical Technology Policy is currently exploring how payors, providers and other stakeholders can work together to generate needed data in a real world setting.

In contrast to IMRT, proton beam therapy was identified as a distinct form of radiation therapy based on different radiobiologic principles of protons compared to photons. Proton beam therapy has not yet widely diffused into the general practice of radiation oncology. Given these two distinguishing factors, proton beam therapy may be a better focus for data collection, clinical trials and technology assessment.