

INTENSITY MODULATED RADIATION THERAPY:

Next Generation 3-D CRT or Distinct Form of RT?

Three dimensional conformal radiation therapy (3D-CRT) uses a uniform dose of radiation where the dose distribution is shaped to conform tightly to the shape of the tumor. In contrast, intensity modulated radiation therapy (IMRT) delivers non-uniform beam intensities to the target volume. (Kuban and Dong, 2004). Specifically, in IMRT non-uniform intensities are assigned to tiny subdivisions of beams, called “beamlets,” enabling custom dosing of optimum dose distributions. For example, if a normal structure overlaps the planning target volume (PTV), one would ideally like to reduce the intensity of those radiation rays that pass through the normal structure. However, using this strategy the target volume would have a “cold spot” of decreased intensity in the shadow of the normal structure. To compensate for this shadow, the intensities of other rays in other beams would need to be increased. While conventional radiation therapy uses wedges and compensators to provide intensity modulation, the unique aspect of IMRT involves the use of a computer-aided optimization process to determine the non-uniform intensity distributions to attain certain specified clinical objectives. Using IMRT, the target volume can be treated with different fraction sizes simultaneously. This contrasts with conventional radiation therapy, in which the same fraction size is used for all target volumes, but the field sizes are reduced in stages over critical regions in order to protect critical normal structures. The basic premise and promise of IMRT is that sculpting the radiation to the target volume more precisely will result in 1) a decrease in the exposure in the surrounding normal tissues, thus reducing acute toxicity; and 2) the ability to increase the dose to the tumor target, thus potentially reducing local recurrence rates.

IMRT can be delivered with a variety of devices, i.e. using multiple beams from fixed angles or rotating beams, frequently using a multi leaf collimator (MLC). As the radiation beam exits the linear accelerator, the collimators block or “collimate” the beam edges to define the radiation field size—its width x length. In older accelerators there were 2 pairs of collimators—right/left; top/bottom. The MLC (a recent innovation) divides one pair of collimator blocks into strips, called leaves, which are typically 0.4 to 1.2 cm in width. This allows the edges of the radiation field to be shaped on the right and left, rather than being a straight edge. The leaves can even move during treatment, varying the distance or aperture between the pairs of right/left leaves. To deliver IMRT, a computer varies the aperture size continuously and independently for each MLC leaf pair, dividing the beam into “beamlets.” The beam may remain “on” as the linac with its MLC moves around the patient, referred to as dynamic MLC, or may be turned off during movement and then turned on once the linac reaches prespecified positions (i.e. step and shoot technique).

“Tomotherapy” is a very different option for IMRT delivery, and consists of a small radiation portal that moves spirally around the patient with varying intensity. Conceptually, it is like a diagnostic spiral CT scanner modified to deliver the higher radiotherapy energies and equipped with IMRT delivery software. In fact, the machine looks like a CT scanner and can perform

diagnostic CT scans (using higher radiation therapy energies) of the treatment field before each treatment, a quality assurance process called Image-Guided Radiotherapy (IGRT).

Compensator-based IMRT is a technically simpler but more labor intensive technique that can be adapted to existing linear accelerators. Instead of using MLC, a compensator can be customized into a three-dimensionally sculpted block that looks like a 3-D geographical map. In fact, this is a radiation compensation map that carries the intensity modulation information. This compensator device requires fabrication for each radiation field, which is costly and time consuming prior to beginning a therapy course. During the treatment course, the compensators must be manually inserted into the tray mount of the linear accelerator for each field. The delivery is also more time-consuming since a radiation therapist must enter the treatment room to exchange customized compensators between treatment fields. However, this treatment method is highly reliable, and can be used with older linear accelerators without MLC, thereby avoiding costly machine replacements. It may be a useful approach for smaller radiotherapy clinics that have older equipment available to them, or for the occasional use of IMRT.

The National Cancer Institute (NCI), in a document describing guidelines for the use of IMRT in clinical trials, defines IMRT as follows:

“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 (multileaf collimator) system using either “sliding window” (DMLC) or “step and shoot” (SMLC) modes; note, this definition also includes techniques with compensators designed by inverse planning, to create a highly conformal dose distribution. The IMRT plans include dose planning objectives and constraints, criteria for target and critical structure expansions, 3D dose distributions, dose volume histogram analysis for targets and critical structures, and plan verification.” (National Cancer Institute 2005)

The various steps in the IMRT planning are defined as follows:

1. Identification of the target

IMRT requires a detailed understanding of the radiographic anatomy in order to correctly identify both the tumor and target volumes and also the structure at risk. Initial planning involves the use of 3D CT images to identify the volume of interest, i.e. the tumor and normal organs. Three different target volumes are identified; 1) the gross tumor volume (GTV), which is based on various images; 2) the clinical tumor volume (CTV), which is slightly larger than the GTV to include subclinical disease; 3) the planned tumor volume (PTV), which is in turn larger than the CTV. The PTV takes into account both interfraction and intrafraction movement. For example, the location of the prostate may vary both with patient positioning (interfraction) and also vary slightly with breathing or other patient movement (intrafraction). To accommodate for this uncertainty, treatment margins are extended to ensure that the prostate is adequately radiated, referred to as the planning tumor volume (PTV). While the GTV and CTV are independent of the type of radiation delivery, the PTV may be closer to the CTV using IMRT, assuming a more precise treatment planning. In addition, a variety of techniques designed to control for patient movement, discussed further below, may also permit a PTV closer to the CTV. IMRT techniques permit the delineation of sharp boundaries between target tissue and the organs at risk.

However, this also means that IMRT treatments are much more sensitive to geographic uncertainties compared to 3D CRT techniques.

2. Specification of the treatment objectives and optimization of intensity distributions

Conventional radiation therapy, including conformal radiation therapy, is based on "forward planning," which starts with the definition of the 3D beam geometry, followed by calculation of the 3D dose distribution. The planner first defines a radiation beam configuration and then the radiation dose distribution is calculated using a computer algorithm. The planner then evaluates the dose distribution and if it is judged to be unacceptable, changes are made to either the beam geometry or other parameter. For example, the initial geometry of the beam can be modified (i.e. by changing the beam weights, adding another beam, using beam modifiers) in order to improve the target dose coverage or decrease the dose to critical area. This process continues in an iterative trial and error fashion until a satisfactory plan is generated.

In contrast, the starting point for the inverse planning of IMRT is delineation of the desired dose distribution, rather than how a final dose distribution will be achieved. This strategy is referred to as "inverse planning." The planner must not only define the target volume but also the desired dose and degree of inhomogeneity and other constraints, such as the tolerance of various critical normal tissues. Collectively these parameters are known as the optimization criteria. In the next step, an IMRT optimization program iteratively adjusts beam parameters to identify that combination that will most closely achieve the selected dose distribution. The optimization software is based on one of several mathematical formulas and algorithms.

3. Treatment design

The plan optimization process is then used to design the leaf trajectories (i.e. the leaf motion sequences or positions of the leaves).

4. Quality assurance

IMRT beams have areas of high dose gradients, not only at the boundaries of treatment, but anywhere in the field. Therefore, IMRT requires strict quality assurance to ensure that the calculated dose distributions will actually be delivered. The most stringent level of quality assurance requires mapping the plan fields onto a phantom and comparing the results with the measurements made on the phantom. It is assumed that the results on the phantom can be extrapolated to the patient.

In 2005, the National Cancer Institute (NCI) developed guidelines for the use of IMRT in clinical trials. These guidelines included extensive requirements for IMRT quality assurance as follows (National Cancer Institute, 2005):

"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 Oncology Group (ROG) QA center, the Radiological Physics Center (RPC) and the Resource Center for Emerging Technologies (RCET). The ATC is responsible for building the 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 the

QA process and one pathway for credentialing is the IMRT questionnaire and benchmark developed by QARC and adopted by the ATC. 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 patients. 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 phantoms before shipping it back to the RPC for analysis. The phantoms contain imageable objects definable as 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."

5. Fractionation schedules

Conventional doses of radiation therapy typically involve 70-75 Gy delivered in 35-41 fractions. Recently hypofractionated dose schedules have been investigated, based on new understanding of the radiobiology of prostate cancer, suggesting that prostate cancer possesses higher fractionation sensitivity. (Brenner 1999, 2002, Fowler, 2001) This means that the use of hypofractionation (i.e. larger dose per fraction and less number of fractions) may provide an improved therapeutic ratio by reducing toxicity to surrounding tissues, while maintaining the same level of local tumor control. The reduced number of fractions also presents a convenience to the patient. It should be noted that hypofractionation is a strategy that can also be applied to 3D-CRT, but when applied to IMRT, the technique is referred to as SC-IMRT (short course IMRT).

6. Patient/Prostate Immobilization Techniques, Image Guided RT

A fundamental principle of radiation therapy is that success is related to optimal alignment of the treatment field to the target volume. This parameter is particularly important for IMRT. For example, IMRT techniques treat only a portion of the planned tumor volume at a time, and therefore, IMRT delivery is very sensitive to patient movement during treatment. This issue is further complicated by the fact that IMRT delivery is longer compared with 3D CRT so that the patient must remain immobile for a longer period of time. Various strategies of controlling for interfraction and intrafraction movement have been investigated. For example, treatment planning based on static CT scans cannot take into account the temporal-spatial variations in the treatment region owing to set-up uncertainties, but also cannot take into account changes in the prostate location due to patient movement or physiologic activity. Immobilization of the patient

and prostate is one obvious strategy to maintain conformality, and various techniques are used ranging from thermoplastic casts to ensure the same patient position, and the use of endorectal balloons, which can help to immobilize the prostate internally.

An alternative strategy is to modify the RT to conform to the target as it changes position either during or between treatment, collectively referred to as image guided RT. Treatment verification can be achieved using an electronic portal imaging device (EPID), which relies on bony anatomy and thus cannot provide soft tissue verification. Several enhancements have been developed. For example, daily transabdominal ultrasound has been used for image guidance, referred to as B.A.T. (**B** mode **U**ltrasound **A**cquisition and **T**argeting). This system correlates the prostate position to the planning information and allows for position correction before each fraction. Radio-opaque markers can be easily implanted in the prostate gland to improve treatment verification. The implanted markers can permit tracking and gating of radiation treatment to the prostate. (Pouliot 2003) Mega- and kilovoltage cone-beam CT scanners have also been integrated onto the gantry of a linear accelerator, which permit CT-quality image acquisition and reconstruction in a short time with the patient in the treatment position. Both of these systems permit interfraction adjustment based on the position of the prostate gland. The next step is intrafraction adjustment, which implies automatic modification of the treatment beams to account for slice to slice anatomic variations due to respiratory movements or other patient movement.

It should be noted that all of the strategies for patient and prostate gland immobilization can apply to both 3D-CRT and IMRT, and that many image guided approaches also apply to both RT techniques.

The proposed advantages of IMRT include the following:

- Higher level of conformation (i.e. a sharper fall off at the target volume boundary, thus sparing normal tissues)
- Potential for further dose escalation
- Efficiency in planning and delivery (i.e. simultaneous treatment of targets requiring high, intermediate and lower doses, "simultaneous integrated boost")

Potential disadvantages include (Esiashvili *et al.*, 2004).

- Prolonged treatment planning process
- Longer treatment delivery time, dose inhomogeneity within the target tissue, which can lead to "cold" spots
- Increased volume of normal tissue exposed to low dose radiation, potentially increasing the long term risk of secondary malignancies.

Advocates of IMRT posit that this technology does not represent a unique form of RT, but rather a natural evolution of 3D-CRT techniques, and given this, that IMRT does not warrant a distinct assessment of safety and efficacy. Certainly IMRT adheres to basic radiologic principles, which have always included attempts to improve dose conformality. However, as noted in the description, IMRT involves an entirely novel planning technique, i.e. inverse planning, compared with the forward planning used in conventional 3D-CRT techniques. Multiple studies have

generated 3D-CRT and IMRT treatment plans from the same initial imaging scans and then compared the predicted dose distributions within the target and in adjacent organs at risk. These studies have documented that IMRT can improve conformality and dose homogeneity compared with 3D-CRT. Dosimetry using stationary targets confirms these results. (De Meerleer 2000, Kao 2004, Luxton 2001, Nutting 2000, Sethi 2003, Zelefsky 2000) These data support the hypothesis that IMRT will reduce acute side effects and may improve local control by reducing under-dosing within the tumor. Advocates of IMRT point to these planning studies as adequate evidence that IMRT will result in a decrease in acute side effects.

However, these planning studies are not a substitute for clinical studies that confirm these effects. The following considerations, adapted from the NCI guidance document for IMRT use in clinical trials, illustrate this point.

- The dose distributions of IMRT are highly complex, potentially leading to unforeseen complications.
- IMRT may involve altered time-dose fractionation and dose heterogeneity for both the target and normal tissues and the radiobiologic parameters of these parameters are unknown. In general, dose heterogeneity increases as the required dose gradient between the target and an adjacent critical structure increases, the distance between the target and a critical structure decreases, and the number of available beam directions decreases.
- 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.
- With IMRT using inverse planning, the target must be outlined precisely or it might not be treated to the prescribed dose. If a critical structure is not outlined, it might not be spared. 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.
- IMRT plan evaluation requires more diligence than does traditional 3D-CRT planning. IMRT can create cold spots or hot spots in unexpected locations, which are not easily appreciated on dose volume histograms (DVH). IMRT plan evaluation requires inspection of isodose distributions on each image slice.
- The conformal dose distribution and high dose gradients of IMRT require patient immobilization as well as quantitative assessment of target and organ motion detection and control. IMRT techniques treat only a portion of the target volume at a particular time, and there is a potential for significant dosimetric consequences if the patient and/or target volume move during treatment. The risk of movement is increased because of the longer treatment time of IMRT compared with 3D-CRT, requiring the patient to remain in a fixed position for longer periods of time. Small movements in the patient or organ can result in significant deviations from the calculated doses.

- The optimization of ray intensities is based on one of several mathematical formulas and algorithms, each of which has unique strength and weaknesses. The beamlets of IMRT have varying intensities. Therefore, the mechanical accuracy of the IMRT delivery system and accurate modeling of machine parameters is very important. These 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. The instrumentation and methods used for quality assurance for IMRT (i.e. ensuring that the planned dose is what is delivered) are not yet well established.

Risk of Secondary Malignancies

There is an abundance of data to show that radiation therapy can induce cancer in humans. Based on an analysis of SEER data between 1873 and 1993, an increased incidence of second malignancies was observed in prostate cancer patients undergoing radiation therapy compared with radical prostatectomy consistent with radiobiologic principles. (Brenner 2000). In absolute terms, the estimated risk of developing radiation associated second malignancies was 1 in 70 in those surviving longer than 10 years. Greater than 10 year survival times are not unusual for prostate cancer and may be increasing due to the increased detection of early stage prostate cancer associated with PSA screening. These results occurred prior to the introduction of more precise radiation techniques, and were based on techniques that exposed larger volumes of tissue to radiation treatment than occurs with modern high energy, conformal technologies. Second malignancies may emerge as a more significant issue associated with an increasing incidence of early diagnosis.

Compared to 3D-CRT, IMRT exposes smaller volumes of tissue to higher radiation doses, and exposes larger volumes of tissue to lower radiation doses. Therefore, IMRT may reduce the risk of second cancers by reducing the volume of tissues treated to high doses. Alternatively, there is a concern that compared with 3D-CRT, IMRT may further increase the risk of second malignancies because of exposure of larger volumes to lower doses. (Eschivalli 2004, Urbano and Nutting, 2004; Glatstein, 2002). In addition, the amount of radiation leakage is related to the amount of beam “on-time,” which is considerably longer for IMRT compared with 3D-CRT. For example, in the step and shoot method of delivery, the beam on-time is 4 times greater than 3D-CRT. (Kry 2005) Both factors may lead to an increase in second cancers. The most common technique used to estimate the risk of developing secondary malignancies is based on the risk coefficient compiled by the National Council of Radiation Protection and Measurement (NCRP). These risk coefficients represent the absolute risk of developing a fatal secondary malignancy based primarily from data from Japanese atomic bomb survivors. Using this data, Hall and Wu estimate that the incidence of second malignancies will increase from 1% to 1.75% for patients surviving 10 years (Hall and Wu, 2003). Kry and colleagues calculated the risk of fatal second malignancies for 6 different IMRT approaches. (Kry 2005) The conservative maximum risk was 1.7% for conventional radiation, 2.1% for IMRT using 10 MV x-rays, and 5.15 using 18 MV x-rays. Younger men more typically elect prostatectomy, while older men and those with comorbidities select RT, suggesting that an increased risk of a second malignancy may not be a great concern for those with a limited baseline life expectancy. However, IMRT and associated image guided techniques may make RT a more attractive option to younger men. Given the large

and increasing number of men diagnosed with clinical localized prostate cancer and excellent prospects for long term survival, even a small increase in risk could lead to a significant total number of second cancers in a cohort of men who otherwise would likely have a favorable prognosis. Similarly, a technique such as IMRT that could reduce the chance of secondary malignancy could have a substantial benefit in the general population.

Summary:

It is clear that IMRT offers the opportunity of more conformal dose distributions and for that reason IMRT is sometimes presented as a natural evolution of 3D-CRT techniques. However, the NCI refers to IMRT as a “new paradigm in radiation therapy.” As outlined above, there are significant differences in both IMRT planning and delivery that create unique and important issues of safety and effectiveness, particularly if IMRT is seen as an alternative to current applications of 3D-CRT or brachytherapy. Given the complex quality assurance required, an additional question is whether the results reported from experienced centers can be duplicated elsewhere. Additionally, if IMRT is adopted as the routine RT technique for all prostate cancers, the increased risk of secondary malignancies from low doses of radiotherapy becomes an increasing concern for younger men with early stage prostate cancer who can be effectively treated with 3D-CRT or brachytherapy.

Intensity Modulated Radiation Therapy (IMRT) for the Treatment of Localized Prostate Cancer

BACKGROUND

Prostate Cancer

In 2006, approximately 234,000 new patients will be diagnosed with prostate cancer and about 27,000 men will die of the disease (Jemal et al. 2006). This makes prostate cancer the most common malignancy in men in the U.S. after skin cancer and the second most common cause of cancer death second only to lung cancer. In spite of these figures, there is ongoing controversy surrounding the role of screening for prostate cancer and the appropriate treatment for men diagnosed with clinically localized disease. Recommendations for the use of prostate specific antigen (PSA) in screening for prostate cancer have been advanced by the American Cancer Society and the American Urological Association (<http://www.cancer.org>; <http://www.urologyhealth.org/adult/index>). However, the U.S. Preventive Services Task Force (USPSTF) has concluded that the evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA testing or digital rectal examination (DRE). The USPSTF found good evidence that PSA screening can detect early-stage prostate cancer but also found mixed and inconclusive evidence regarding early-detection improvement in health outcomes.

Screening is associated with important harms, including frequent false-positive results and unnecessary anxiety, biopsies and potential complications of treatment of some cancers that may never have affected a patient's health. Despite the uncertainties in the long term effectiveness of PSA screening, PSA screening is widely offered and is credited with the increasing incidence of prostate cancer, and an increase in the incidence of early stage prostate cancer. The distinction between clinically significant and indolent prostate cancer is still poorly understood, which makes treatment choices very complex.

Many men present with clinically localized prostate cancer, i.e. without evidence of spread to the lymph nodes or distant metastases. Clinically localized disease encompasses a heterogeneous group of tumors, which are further subdivided into the following categories:

T1: Clinically unapparent tumor neither palpable nor visible by imaging

- T1a: tumor incidental histologic finding in 5% or less of tissue resected
- T1b: Tumor incidental histologic finding in more than 5% of tissue resected
- T1c: Tumor identified by needle biopsy (e.g. because of elevated PSA).

T2: Tumor confined within the prostate

- T2a: Tumor involves one half of one lobe or less
- T2b: Tumor involves more than one-half of one lobe but not both lobes
- T2c: Tumor involves both lobes

T3: Tumor extends through the prostatic capsule

- T3a: Extracapsular extension (unilateral or bilateral)
- T3b: Tumor invades the seminal vesicles

T4: Tumor is fixed or invades adjacent structures other than seminal vesicles

A key element of treatment planning is the assessment of the risk of extraprostatic spread and involvement of the seminal vesicle or lymph nodes. For example, radiation therapy may be more extensive if there is a high risk of extraprostatic spread or seminal vesicle involvement, and patients with a high risk of lymph node involvement may receive either radiation to the pelvic lymph nodes or a pelvic lymph node dissection. Androgen deprivation therapy may also be offered to those at high risk of lymph node involvement. Nomograms have been developed to help assess risk, and are based on the PSA level, the Gleason score and PSA level. (Partin 2001) Definitions of low, intermediate and high risk disease vary across studies, but the National Comprehensive Cancer Network (NCCN) defines the risk levels as follows:

Low:

T1-T2a AND Gleason score 2-6 and PSA < 10 ng/ml

Intermediate

T2b-T2c OR Gleason score 7 OR PSA 10-20 ng/ml

High:

T3a OR Gleason score 8-10 OR PSA > 20 ng/ml.

Treatment options for low risk disease include watchful waiting, hormone therapy, radical prostatectomy, brachytherapy (a common option for low risk disease) or EBRT using either

photons or protons. With the exception of watchful waiting, treatment options for intermediate disease are similar. While there have been no randomized studies of these alternatives, nonrandomized and retrospective studies suggest that there is no significant difference in outcome for the active treatment options. However, there is ongoing controversy regarding the role of dose escalation EBRT for patients with intermediate risk disease, and the role of androgen deprivation therapy (ADT). High risk disease is typically treated with a combination of ADT and radiation therapy.

3D-CRT and Prostate Cancer

EBRT using photons has been a mainstay of treatment of clinically localized prostate cancer. There has been longstanding research interest in increasing the radiation dosage to improve local control rates. However, the incidence of acute and chronic rectal and urinary side effects has been limiting factors. Traditional radiation therapy used unshaped treatment fields developed from orthogonal radiographs and anatomical landmarks. This 2-dimensional technique of treatment planning could not accurately determine the internal position or shape of the prostate gland and its relationship to surrounding organs, resulting in larger treatment volumes and excessive doses to the rectum and bladder. Using 2D planning, typical radiation doses for prostate cancer were 67-70 Gy. However, local recurrence was a common event after conventional doses of radiation therapy, and locally persistent tumor was thought to be a source of metastatic disease. Therefore, there was intense interest in techniques for dose escalation, particularly since retrospective studies suggested a favorable dose response curve. (Hanks 2002)

Three dimensional conformal radiation therapy (3D-CRT) was introduced in the 1990s and revolutionized the treatment planning for radiation therapy. Detailed 2D images of the prostate gland can be stacked to create 3D models in spatial relationship with surrounding organs. The radiotherapy treatment portal can then be shaped to the projected profile of the prostate target volume within the axis of the radiation beam, referred to as the beam's eye view (BEV). (Khoo 2005)

Results of randomized studies showed that 3D-CRT at standard doses resulted in decreased morbidity compared with 2D planning, setting the stage for dose escalation studies, (Dearnaley 1999 Koper 1999) particularly in patients with intermediate and high risk disease. Results of three randomized controlled trials have now been reported suggesting that dose escalation is associated with improved biochemical outcomes, based on PSA levels. For example, Pollack and colleagues compared the outcomes of 70 Gy with conventional radiotherapy vs. 78 Gy using 3D-CRT in 305 patients with T1-T3 disease. (Pollack 2002). The primary endpoint was freedom from failure (FFF), as detected clinically or biochemically by three rises in the PSA level. The FFF rates for 78 Gy vs. 70 Gy at 6 years was 64% and 70%, respectively. The dose escalation preferentially benefited those with a PSA of 10 or greater. The incidence of rectal side effects were higher in the 78 Gy group, with toxicity rates of grade 2 or more in 26% of patients in the 76 Gy group compared with 12% in the 70 Gy group. In another randomized controlled trial, Zeitman compared either 70.2 Gy or 79.2 Gy in 393 patients with Stage T1b through T2b prostate cancer; patients were followed for 5 years. (Zeitman 2005) The higher dose was delivered using a combination of photon and proton beams. The proportions of men free from biochemical failure at 5 years were 61.4% for conventional dose and 80.4% for high dose therapy ($p < .001$). In contrast to the Pollack study, both patients with high and low risk disease benefited from dose

escalation. There was a 2% incidence of Grade 3 acute urinary or rectal toxicity in the high dose group compared with 1% in the conventional dose group. Finally, Peeters and colleagues reported on the results of a trial that randomized 669 patients with T1b-4 disease to receive either 68 Gy or 78 Gy 3D-CRT. Hormone therapy was prescribed in 143 patients. (Peeters 2006) The primary outcome was freedom from failure (FFF), as defined clinically or biochemically (i.e. PSA levels). Biochemical FFF was significantly better in the 78 Gy arm compared with the 68 Gy arm (64% vs. 54%). Results were not presented separately for different risk levels. While the increase in acute toxicity related to increased dose has been considered to be tolerable, studies are now emerging of the long term side effects. For example, Heemsbergen and colleagues have reported that acute GI toxicity is a significant predictor of late toxicity. (Heemsbergen 2006)

None of these studies reported improvements in overall survival, which is perhaps not surprising given the long natural history of prostate cancer and follow ups of 4-6 years. Taken together, these results suggest that dose escalation to 78-79 Gy is associated with improved biochemical outcomes with acceptable complication rates, particularly in men with intermediate and high risk clinically localized prostate cancer. IMRT has been investigated as technique to further reduce the acute side effects in doses up to 78-79 Gy, and as a technique to permit further dose escalation.

IMRT and Prostate Cancer

IMRT with its enhanced conformity and steep dose gradients offers the potential of dose escalation beyond that possible with 3D-CRT while achieving lower toxicity (Esiashvili 2004). IMRT is particularly suited to dose escalation in prostate cancer as it can minimize high dose exposure to the rectum, bladder, penile bulb and femoral necks while allowing for higher total dose to the prostate. (Jani 2003) Three general indications for IMRT have been suggested for the treatment of prostate cancer:

- IMRT as an alternative to 3D-CRT at doses up to 79 Gy.
Improved outcomes with acceptable acute side effects have been demonstrated for radiation doses up to 79 Gy using 3D-CRT. Therefore, at this radiation dose, the incremental value of IMRT primarily relates to a potential decrease in acute and chronic toxicities.
- IMRT as a unique treatment for RT delivery for doses 80 Gy and above.
However, further dose escalations to 80 Gy and above, referred to as “ultra high dose” are only possible using IMRT. In this setting the incremental value of IMRT relates to possible further reductions in local recurrence rates balanced against the incidence of side effects.
- IMRT as an alternative to 3D-CRT as a technique to irradiate the pelvic lymph nodes in intermediate and high risk patients to reduce the risk of subsequent metastatic disease.
- IMRT as a technique to deliver altered fractionated schedules.
Hypofractionation of RT has been a research interest for many years. Hypofractionation offers the advantages of a shorter course of therapy and potentially offers an improved therapeutic ratio. Both 3D-CRT and IMRT has been used as a technique for hypofractionation.

Other evolving aspects of radiation therapy in general include a variety of immobilization techniques and image guided radiation therapy, both designed to further reduce complication rates.

ASSESSMENT PARAMETERS

An assessment of IMRT for prostate cancer potentially encompasses a wide variety of variables, including patient variables, tumor variables, and RT planning and delivery variables. Individual consideration of each of the many combinations of these factors is beyond the scope of this assessment. The following discussion defines the more limited parameters used in this assessment.

1. Radiation Techniques

This assessment focuses on the use of IMRT as an alternative to 3D-CRT as initial treatment of clinically localized prostate cancer. Only studies using photon beams will be considered; i.e. proton beam therapy is not a focus of this assessment. For the purposes of this assessment, different delivery techniques of IMRT, i.e. multileaf collimators, tomotherapy and compensator-based are not considered separately. Different techniques to correct for daily set up errors and inter- and intrafraction organ motion are also not considered separately. These techniques include various different immobilization strategies (thermoplastic casts, endorectal balloons, etc) and various techniques of image guidance integrated into treatment machines, such as transabdominal ultrasound based imaging, imaging of implanted radio-opaque markers using electronic portal imaging devices and integrated online computed tomography. All of the above strategies are not unique to IMRT, but can also be adapted to 3D-CRT.

2. Clinical Outcomes

Outcomes assessed in trials of prostate cancer treatment include cancer control, morbidity, quality of life, salvage of primary treatment failures, late effects and cost. Of these, cancer control is probably the most important but may be the most difficult to assess because of the long natural history of the disease. In the past, cancer control was determined by the absence of local progression on physical examination or prostate biopsy, metastatic disease or cancer related death. More recently, biochemical failure has been accepted as the most accurate end-point for comparing the efficacy of various treatments, even though there is not sufficient data to support biochemical failure as a surrogate for survival and there is not always overt metastatic disease present in men with a rising PSA (Klein and Kupelian, 2003). Unlike radical prostatectomy where serum PSA levels are expected to be undetectable, detectable PSA levels are expected after RT, even if all tumor is eradicated (since some normal prostate epithelium survives radiation). However, nadir serum PSA is a good indicator of treatment success following RT. A consensus panel of the American Society for Therapeutic Radiology and Oncology recommends that three consecutive rising levels, after a nadir or a rise high enough to trigger hormonal treatment, be considered a recurrence. (ASTRO Consensus Statement, 1997). Therefore, the key clinical outcome studied in this assessment is the biochemical failure rate defined by serial measures of PSA levels. The incidence of both acute and long term rectal and bladder complications, including the risk of secondary malignancies are key clinical safety outcomes.

Assessment Questions:

1. Compared with 3D-CRT, at radiation therapy doses up to 79 Gy, is IMRT associated with a reduction in acute and chronic toxicities?
2. Is IMRT at doses of 80 Gy and higher associated with improved biochemical control and acceptable acute and long term side effects?
3. Is IMRT of the pelvic lymph nodes associated with a decreased incidence side effects compared with 3D-CRT?
4. What is the safety and effectiveness of hypofractionation using 3D-CRT or IMRT?

The *MEDLINE database* was searched through July 2006 using the search terms “prostate cancer”, “intensity modulated radiation therapy”, “IMRT”, “conformal radiation therapy”. Articles reporting on results of clinical trials were retrieved. In addition, review articles and systematic reviews on treatment of prostate cancer in general and specifically on radiotherapy and IMRT, were retrieved.

Question 1:

Compared with 3D-CRT at radiation therapy doses up to 79 Gy, is IMRT associated with a reduction in acute and chronic toxicities?

In the 1990s, RT techniques transitioned from 2D planning to 3D-CRT, in part prompted by the anticipated reduction in acute side effects. There were two randomized controlled trials that specifically investigated the ability of 3D-CRT to reduce acute complications compared with 2D techniques. For example, Dearnaley and colleagues compared the acute side effects associated with 3D-CRT and conventional 2D techniques delivered to the same dose of 64 Gy. For those in the 3D-CRT arm, there was a significant reduction in late radiation sequelae, such as rectal proctitis. (Dearnaley 1999). Koper and colleagues randomized 266 men to receive either conventional 2D techniques or 3D-CRT to a prescribed dose of 66 Gy. (Koper 1999) The incidence of grade 2 gastrointestinal toxicity was 19% in the 3D-CRT arm compared with 32% in the conventional arm. While the transition from 3D-CRT to IMRT has also been prompted by an anticipated reduction in side effects, there are currently no controlled clinical trials comparing the acute toxicities of IMRT and 3D-CRT. As discussed above, 3D-CRT has been the focus of dose escalation studies, and doses up to 79 Gy have been given, with acceptable morbidity. Therefore a relevant question is whether IMRT will increase the safety profile of 3D-CRT at this dose level.

No studies have compared the acute and chronic toxicities of IMRT and 3D-CRT in a randomized fashion in patients with prostate cancer. Several IMRT planning studies have investigated the dosimetric and theoretical clinical advantages of IMRT over 3D-CRT (De Meerleer 2000, Kao 2004, Sethi 2003). However, data from non-randomized trials allows some comparison of the complication rates of 3D-CRT and IMRT at comparable doses.

Perhaps the most extensive experience with IMRT has been published by Memorial Sloan Kettering Cancer Center. In their most recent update, investigators presented their long term toxicity for dose groups of 70.2 Gy, 75.6 Gy and 81 Gy. (Shippy 2006). The majority of patients receiving 81 Gy received IMRT while the other two groups received 3D CRT. The rate of 10 year grade 2 rectal toxicity was 5%, 19% and 3% for <70.2 Gy, 75.6 Gy and 81 Gy, respectively. The lowest rates of rectal toxicity were associated with IMRT, even though the radiation dose was higher.

Su and colleagues presented the GI and GU toxicity results of a single institution case series of 461 patients receiving either IMRT (n=106) or conventional 3D-CRT (n=355). (Su et al. 2006) Both groups were well balanced regarding age, race, PSA and hormone use. However, the IMRT group had a higher median Gleason score, lower percentage of T3/4 disease and received a higher dose (76 Gy vs. 70 Gy) compared to the 3D-CRT group. Follow up was similar in both groups; a median of 29.3 months for IMRT group compared to 26.4 months for those receiving 3D-CRT. Although the IMRT group received a higher dose of RT, the incidence of GI toxicity was less. For example, the incidence of Grade 1 toxicity was 9% in the IMRT group compared to 25% in the 3D-CRT group and Grade 2 toxicity was 3% vs.8% respectively, while the incidence of Grade 3 and 4 toxicities were similar in the two groups. In contrast IMRT was not associated with a reduction in GU toxicity.

In another single institution case series, Kirichenko and colleagues compared the morbidities of 489 patients treated with IMRT with 928 patients treated with 3D-CRT. The patients were well matched for PSA, t-stage and Gleason score. The median follow-up for the IMRT group was 30 months, compared to 63 months for the 3D-CRT group. Those receiving IMRT received doses ranged from 74-78 Gy, while those receiving 3D-CRT received doses ranging from 70-79 Gy with a median of 72 Gy. The acute GI and GU toxicity did not differ between the IMRT and 3D-CRT group. However, IMRT was associated with a decreased risk of later GI toxicities. At three years the actuarial risk for late 2 or greater GI toxicity was 10.4% for 3D-CRT compared to 6.2% for IMRT. Late GU toxicity was slightly increased in the IMRT group with a three year estimated rate of 8.4% compared to 5.7% or 3D-CRT. This difference disappeared after controlled for significant predictors such as TURP and BPH. Other controlled studies of 3D-CRT at a dose of 78 Gy have reported rectal toxicities of grade 2 or greater in 26-32% of patients with a follow up of 51 to 60 months. (Pollack 2002, Peeters 2006)

These studies provide some indirect support for the assertion that at 3 year follow up, IMRT may be associated with a reduction in grade 1-2 GI toxicity, with no difference in GU toxicity. However, multiple different patient factors, different radiation dosages and different time frames for reporting toxicities prevent any detailed analysis.

Literature Gap:

Various planning studies using dose volume histogram (DVH) analysis have reported that, compared with 3D-CRT, IMRT is consistently associated with greater sparing of adjacent normal tissues, including the rectum, bladder and penile bulb. From an evidence based point of view, these planning studies would be considered an intermediate outcome, which would require confirmation in further controlled studies. Other case series of IMRT have reported a low

incidence of acute rectal toxicity compared to similar doses of 3D-CRT, but currently there are no completed or ongoing controlled clinical trials specifically designed to address this question.

Question 2:

Is IMRT at doses of 80 Gy and higher associated with improved biochemical control and acceptable acute and long term side effects?

In an initial feasibility study, Zelefsky et al. reported on the acute and late toxicities of high dose radiation (81Gy) in 61 patients with clinical stage T1c-T3 prostate cancer treated with 3D-CRT and 171 patients treated with IMRT, between September 1992 and February 1998. (Zelefsky 2000) They report a two-year actuarial risk of Grade 2 rectal bleeding of 2% for IMRT and 10% for 3D-CRT ($p<0.001$). The combined rates of acute Grade 1 and Grade 2 rectal toxicity (according to the Radiation Therapy Oncology Group toxicity scale) were 79/171 (45%) in the IMRT group and 37/61 (61%) in the 3D-CRT group ($p=0.05$). There was one patient in each group (IMRT and CRT) with Grade 3 rectal toxicity (bleeding that requires laser cauterization). Acute and late urinary toxicities were not significantly different between the groups. The authors conclude that the data demonstrate the feasibility and safety of high dose IMRT for localized prostate cancer. No information is provided regarding how patients were assigned to each treatment group. Outcomes on sexual dysfunction are not reported. No patient satisfaction or quality of life data are presented.

The above study was followed by a large case series of 1,100 patients treated with 3-D CRT or IMRT, where results included both acute toxicity and biochemical relapse free survival (RFS) (Zelefsky 2001). This study included overlapping patients with the initial feasibility study. The study was initiated in 1988 and completed in 1998. During that time, the radiation dosage was increased from 64.8 to 86.4 Gy in increments of 5.4 Gy. A total of 9% received 64.8 Gy, 24% received 70.2 Gy, 40% received 75.6 Gy, 23% received 81 Gy and 4% received 86.4 Gy. 3D-CRT was used to deliver RT in all patients up to 75.6 Gy, and in the first 61 of the 250 patients treated with 81 Gy. The remaining 189 received IMRT, as well as all 40 patients receiving 86.4 Gy. Biopsies were performed 2.5 years or greater after treatment. Patients were categorized into prognostic risk groups based on pre-treatment PSA, Gleason score and clinical stage. The authors reported a significant reduction in the incidence of late Grade 2 rectal toxicity in the patients treated to 81Gy with IMRT compared with 3D-CRT (2% vs. 14%). In favorable and intermediate risk levels, a significant improvement in PSA outcome was associated with 75.6 Gy compared with lower doses. However, in this same group of patients there was no difference in PSA relapse free survival in patients treated with 81 Gy compared with 75.6 Gy. Focusing on the unfavorable risk category, 81 Gy was associated with improved PSA relapse free survival compared with 75.6 Gy. In this group the 5 year relapse free survival rate for 81 Gy was 67% compared with 43% for 75.6 Gy and 21% for 64.8 to 70.2 Gy.

A third study from the same group of investigators reported on acute and late toxicity and preliminary biochemical outcomes in 772 patients with clinically localized cancer treated between April 1996 and January 2001, and presumably included overlapping patients from the previous studies. (Zelefsky 2002) In contrast to the previous study, all patients in this study were treated with IMRT. A total of 698 patients were treated to 81Gy and 74 patients were treated to 86.4 Gy. The median follow-up was 24 months. Thirty-five patients (4.5%) developed acute Grade 2 rectal

toxicity (Radiation Therapy Oncology Group criteria) and no patient experienced acute Grade 3 or higher toxicity. Two hundred and seventeen patients (28%) developed acute urinary retention (Grade 3), 76 (10%) developed Grade 2 chronic urethritis requiring medication for symptom control at a median of six months after completion of IMRT and five patients developed a urethral stricture requiring dilation. Eleven patients (1.5%) developed Grade 2 rectal bleeding and four patients developed Grade 3 rectal toxicity requiring transfusions and/or cauterization. Of the patients who were potent prior to treatment, 52% maintained their potency. The three-year actuarial PSA RFS rates for favorable, intermediate and unfavorable risk group patients were 92%, 86% and 81%. Long term results and late toxicity were reported in 2006. (Zelevsky 2006). This overlapping case series included 561 patients with clinically localized prostate cancer treated to a dose of 81 Gy with IMRT. Median follow up was 7 years. The 8 year actuarial PSA relapse free survival rates for patients in favorable, intermediate and unfavorable risk groups were 85%, 76%, and 72%, respectively. The 8 year actuarial likelihood of grade 2 rectal bleeding was 1.6%, and 8 year likelihood of late grade 2 and 3 urethral strictures were 9% and 3%, respectively. The authors concluded that these ongoing follow up studies continue to support the excellent long-term tumor control outcomes and safety of IMRT at a dose of 81 Gy.

These large case series suggest that at doses of 81 Gy, IMRT is associated with decreased incidence of acute toxicity compared with 3D-CRT and that doses of 86.4 Gy are only feasible using IMRT techniques. There is also a suggestion that based on nonrandomized data that 81 Gy results in improved PSA outcomes in patients with prostate cancer and unfavorable risk factors. While promising, these results must be viewed with caution. These are single institution case series, where the results of patients treated with high doses are compared with a noncontemporaneously treated group of patients treated with conventional doses. In this setting, it is difficult to distinguish between the effect of RT dose and other changes in prostate cancer management that occur over time because of the number of time sensitive variables involved in prostate cancer management. (Jacob 2004) For example, stage migration may result from the use of new imaging modalities (i.e. ultrasound, endorectal coil imaging) and sextant or greater number of biopsies. Therefore, a T2b prostate cancer diagnosed today may be different than a stage T2b cancer diagnosed 10 years ago. The definition of biochemical failure, which is time sensitive, also favors more recently diagnosed tumors. (Zeitman 2002) For example, the ASTRO consensus definition of biochemical failure is three consecutive PSA rises. The date of failure is then back dated to the midpoint of the nadir PSA and the first of the three rises. Because of this back dating, the outcome of biochemical freedom from failure looks better with decreasing follow up. (Vicini 1999 Thames 2003). Finally, studies have shown a Gleason score shift migration over the years, with more tumors upgraded to a Gleason score of 6-8, leading to an apparent improvement in biochemical outcome for the most recent cohort. (Chism DB 2003)

Literature Gap:

Studies of further dose escalation to 80 Gy and beyond are dominated by single institution case series. There are currently no controlled clinical trials comparing conventional to high dose IMRT to determine which, if any, patients benefit from dose escalation, as evidenced by improved biochemical outcomes. The incidence of acute and chronic toxicities is also a concern.

Question 3:

Is whole pelvis radiation therapy (WPRT) using IMRT associated with a decreased incidence of acute and chronic toxicity compared with conventional 3D-CRT?

Pelvic lymph node involvement is associated with a poor prognosis. Untreated, most of these patients progress to distant metastatic disease with poor long term disease free survival rates. Therefore, pelvic node dissection, or whole pelvic irradiation therapy (WPRT) with or without androgen deprivation therapy have been offered to patients at high risk of pelvic lymph node involvement. The risk of nodal involvement can be estimated based on nomograms using tumor size, PSA level and Gleason score. While the general roles of WPRT and androgen deprivation therapy continue to evolve, IMRT has also been suggested as an alternative to 3D-CRT as a technique to decrease acute and chronic toxicity. For example, the target volume of pelvic nodes is concave and using 3D-CRT techniques, the bowel nestled in this concavity will be radiated, thus limiting dosages. However, IMRT may avoid bowel radiation. Nutting and colleagues report on a retrospective planning study to compare, by simulation, conventional EBRT, 3D-CRT and IMRT treatment plans for pelvic lymph node irradiation in 10 men with prostate cancer. (Nutting 2000) They concluded that the mean percentage volume of small bowel and colon receiving >45 Gy was 21%, 18% and 5% for conventional EBRT, CRT and IMRT, respectively. The rectal volume irradiated to > 45 Gy was reduced from 50% for CRT to 6% for IMRT and bladder 52% to 7%. The authors conclude that the reduction in critical organ irradiation seen with IMRT may reduce side effects, but caution that “clinical trials are required to confirm the clinical benefits of these dose distributions.”

The role of WPRT is evolving with studies focusing on different combinations of WPRT and androgen deprivation therapy. The incremental benefit of IMRT vs. conventional RT has not been a focus of these studies.

Literature Gap: No clinical studies were identified that compared the acute and chronic toxicities of IMRT and 3D-CRT for whole pelvic irradiation.

Question 4:

What is the safety and effectiveness of hypofractionation using 3D-CRT or IMRT?

Several case series have been reported on hypofractionation using either 3D-CRT or IMRT techniques. The largest case series with the longest follow-up included 703 men with localized prostate cancer who were treated between 1995 and 1998 using 3.13 Gy fractions. (Livesy 2003) The patients were treated with a 4 field conformal technique to a dose of 50 Gy in 16 daily fractions over 22 days. Five year analysis has been published. The authors point out that the primary focus of this study was the incidence of side effects, particularly rectal side effects. The late bladder morbidity was Grade 0/1: 90%; Grade 2, 9%, Grade 3, 1%. Rectal toxicity was recorded as Grade 0, 65%, Grade 1, 30%, and Grade 2, 5%. There was no grade three toxicity. The disease specific survival at 5 years for good, intermediate and poor prognosis tumors was 96%, 91% and 86%, respectively. The authors concluded that the results using this low dose of RT (i.e. 50 Gy) were comparable with other series of patients using higher radiation doses (67-72 Gy) conventional fractionation schedules.

Kupelian and colleagues have published several studies on hypofractionated IMRT. Since these reports likely include overlapping patients only the most recent 2005 report will be discussed here. (Kupelian 2005). This study included the first 100 consecutive patients with localized prostate cancer treated to 70.0 Gy at 2.5 Gy per fraction over 5.5 weeks. Daily target localization with transabdominal ultrasound was used. At a median follow up of 66 months, the biochemical relapse free survival rate for patients with low, intermediate and high risk disease was 97%, 88% and 70% respectively. These results were compared with 310 consecutive cases treated with conventional fraction 3D-CRT; 65% of these patients received hormonal therapy. The corresponding relapse free survival rate in those with low, intermediate and high risk disease was 93%, 79% and 72%, respectively. With hypofractionation, late rectal toxicity is of greatest concern. The actuarial late rectal toxicity was 3%. The authors conclude that high dose rate fractionation is an alternate method of dose escalation in the treatment of localized prostate cancer. In addition, the schedule is significantly more convenient for the patient due to decreased treatment times.

Literature Gap:

There were no controlled trials identified, and no trials comparing hypofractionation as delivered by IMRT vs. 3-D CRT. As noted below in the summary of pending trials, there are several ongoing randomized studies. However, these studies are not designed to determine the relative merits of IMRT vs. 3-D CRT.

SUMMARY

In the absence of controlled trials there is insufficient evidence that IMRT at doses up to 79 Gy offers any incremental advantage compared with similar doses of 3D-CRT. At doses of 81 Gy and higher, IMRT is designed to decrease the recurrence rate of prostate cancer. There are no controlled trials that confirm this hypothesis. Finally, there are no controlled trials that address the incremental value of IMRT as a technique of whole pelvic radiation therapy. Therefore, there is inadequate evidence that IMRT offers treatment advantages compared with 3D-CRT.

In contrast, advocates of IMRT posit that intermediate planning studies have shown that IMRT is consistently associated with greater sparing of normal tissues while providing equivalent or superior coverage of the prostate compared with 3D-CRT. IMRT advocates further point out that these planning studies should be considered as surrogate level-1 evidence of the treatment benefit of IMRT compared with 3D-CRT. In this analysis, controlled studies comparing IMRT and 3D-CRT at doses up to 79 Gy are considered questionably ethical if the presumption is that the safety of IMRT has already been established based on planning studies. Similarly, during the transition from 2D treatment planning to 3D-CRT, planning studies suggested the superiority of 3D-CRT and there was reported limited enthusiasm for controlled studies to confirm this benefit. Indeed, the two randomized trials that were performed (Dearnaley 1999, Koper 1999) were both small international studies.

As summarized below, IMRT is included in various ongoing clinical trials studying dose escalation and altered fractionation regimens. But there is no study that is specifically designed to compare the toxicity profiles of IMRT and 3D-CRT. For example, the RTOG-0126 trial is a dose escalation trial that randomizes patients between 79.2 Gy and 70.2 Gy. This trial

specifically allows treatment with either IMRT or 3D CRT in both arms of the trial. Currently greater than 80% of patients being accrued to the trial are being treated with IMRT. Therefore, while this important trial is designed to investigate dose escalation, it is not designed to compare IMRT and 3D-CRT in a precisely randomized way.

It is apparent from the design of these studies, and from input from relevant specialty societies, that IMRT as a treatment of prostate cancer has been widely embraced by the medical community and is now considered standard practice by many. A recent survey found that one-third of practicing radiation oncologists already use IMRT in their clinical practice (Mell 2003). However, it is also apparent that IMRT represents a distinct form of technically demanding radiation planning and delivery with large gaps between potential advantages as identified by planning studies, and realized advantages, as demonstrated in clinical trials.

While economic factors are not typically the focus of evidence based clinical reviews, costs are reflected in the priorities set for evidence based reviews. Installation of IMRT technology represents a significant institutional investment, which is reflected in facility reimbursement levels that are 4 to 5 times higher than for conventional external beam. (Kagan 2005) Clearly, this reimbursement environment will drive utilization of IMRT, and similarly, these same factors will prompt careful consideration by third party payors.

PENDING TRIALS

There are a number of ongoing randomized clinical trials of IMRT in prostate cancer (<http://cancer.gov/clinicaltrials>). Unfortunately, none of these trials specifically examine the incremental value of IMRT vs. 3D-CRT at conventional doses, or in the setting of whole pelvic irradiation. No trial examines the outcomes of IMRT at doses rates of 80 Gy and higher.

Dose Escalation Studies

1. Radiation Therapy in Treating Patients With Stage I or Stage II Prostate Cancer (RTOG 0126, Clinical Trial Identifier NCT0033631

This is a phase III randomized study of high (79.2 Gy) vs. standard-dose (70.2 Gy) three-dimensional conformal or intensity-modulated radiotherapy in 1,520 patients with Stage I or II prostate cancer designed to answer the question of which dose of RT is more effective. Patients are stratified according to Gleason score and PSA level and radiation modality (3D-CRT vs. IMRT). Quality of life will be assessed periodically. Patients will be evaluated every three months for two years, every six months for three years and once a year thereafter. The use of IMRT or 3D-CRT is at the discretion of the treating physician. Therefore, this trial is not specifically designed to evaluate the incremental value of IMRT vs. 3D-CRT in a randomized way.

Studies of Radiation Therapy to the Pelvic Nodes

1. A Phase II Prostate Cancer Trial Treating Pelvic Lymph Nodes to High Dose Using IMRT (Clinical Trial Identifier NCT00214136)

This phase II trial of 30 patients examines the clinical feasibility and efficacy of using IMRT to escalate the dose to the pelvic lymph nodes in a short course of radiation therapy. An increased total and biologically effective dose will be delivered to the pelvic lymph nodes (50 Gy at 2 Gy/fraction). The prostate will receive standard “short course” of IMRT of radiation (70 Gy at 2.5 Gy/fraction). The primary outcome is the evaluation of acute and long term tolerances to high dose RT to pelvic lymph nodes.

Studies of Altered Fractionation Schedules

1. Phase III Randomized Study of Hypofractionated versus Conventionally Fractionated Three-Dimensional Conformal or IMRT in Patients with Favorable Risk Stage II Prostate Cancer. (RTOG-0415, Clinical Trials Identifier NCT00331773)

This phase three study with a target accrual of 1,067 patients is designed to compare the disease free survival of patients with favorable risk stage II prostate cancer treated with hypofractionated vs. conventionally fractionated 3D-CRT or IMRT. Patients are randomized to receive either treatment once daily 5 days a week for 8.2 weeks (i.e. 41 treatments) vs. one daily 5 days a week for 5.6 weeks (i.e. 28 treatments). Patients are stratified according to Gleason score, PSA and planned radiotherapy modality (i.e. either 3D-CRT or IMRT). Therefore, this study is not designed to directly evaluate the incremental value of IMRT vs. 3D-CRT.

2. Phase III Randomized Study of Neutron and Photon Radiotherapy versus Photon and Hypofractionated Intensity Modulated Radiotherapy in Patients with Stage I-III Adenocarcinoma of the Prostate (Clinical Trials Identifier NCT00258466)

The objective of this trial is to compare the efficacy of neutron and photon radiotherapy vs. hypofractionated IMRT, in terms of a lower frequency of chronic complication rate, in patients with favorable to intermediate prognosis, stage I-III adenocarcinoma of the prostate. A total of 300 patients will be randomized to receive either neutron radiotherapy followed by photon radiotherapy or photon radiotherapy followed by hypofractionated photon irradiation.

Study of Planning Treatment Volumes

1. Intensity-Modulated Radiation Therapy With or Without Decreased Radiation Dose to Erectile Tissue in Treating Patients With Stage II Prostate Cancer (Clinical Trials Identifier NCT00084552)

This is a phase III randomized study of intensity-modulated radiotherapy with vs. without dose sparing for erectile tissue in patients with Stage T1b-T2c adenocarcinoma of the prostate. Radiotherapy dose ranges from 74 to 76 Gy. This trial is being conducted to determine whether

reducing the dose of radiation to erectile tissue will help prevent erectile dysfunction. Patients will be randomly assigned to one of two groups. Patients in Group 1 will undergo RT, five days a week for up to seven weeks. Patients in Group 2 will undergo RT as in group one, but with reduced radiation doses to erectile tissue. Quality of life will be assessed periodically. Patients will be evaluated at three months and every six months thereafter. There is no comparison to 3D-CRT.

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