

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW
FINAL APPRAISAL DOCUMENT

INTENSITY MODULATED RADIATION THERAPY (IMRT)
FOR LOCALIZED PROSTATE CANCER

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EXECUTIVE SUMMARY

Introduction

Prostate cancer is the most common nondermatologic cancer in men. In 2006, approximately 230,000 new patients in the United States were diagnosed with prostate cancer and 27,000 men died of the disease. The major treatment options for localized prostate cancer include external beam radiation therapy, brachytherapy, surgery, and watchful waiting. Data to compare the long-term survival benefits of these options are limited, and thus the choice of a treatment option for many patients is based on considerations of the potential short and long-term side effects of different treatment options.

IMRT is a form of external beam radiation therapy that uses multiple beam angles and non-uniform beam intensities along with CT based computer planning to conform the radiation to the target organ in order to spare normal adjacent structures. IMRT thus has many similarities with three dimensional conformal radiation therapy (3D-CRT) which also uses CT imaging to construct 3D images to help maintain full dose to the target organ while decreasing the radiation dose to normal tissue. The basic premise underlying the potential advantages of IMRT over 3D-CRT is that sculpting the radiation to the target volume of the cancer more precisely will result in:

- A reduction in acute toxicity to the surrounding normal tissues of the gastrointestinal (GI), genitourinary (GU) and sexual organs
- The ability to increase the dose to the tumor target, thus potentially reducing local recurrence rates.

Professional Clinical Guidelines

The clinical guidelines developed by the National Comprehensive Cancer Network (NCCN) say that IMRT may be used instead of 3D-CRT. The National Cancer Institute 2005 guidelines state that “IMRT is still a nascent technology.” The American Society for Therapeutic Radiation and Oncology (ASTRO) has formally concluded that “IMRT represents the preferred method currently available for the treatment of localized prostate cancer with external beam radiation therapy.”

Previous Systematic Reviews and Technology Assessments

There has not been an AHRQ comparative effectiveness review done on IMRT, nor has Blue Cross Blue Shield TEC evaluated IMRT for prostate cancer. The California Technology Assessment Forum produced a draft assessment in 2005 finding that IMRT did not meet criteria demonstrating improvement in net health outcomes, but this draft finding was never finalized. The National Coordinating Center for HTA in England produced a report in 2003 concluding that “the quality and paucity of evidence and the reliance on the reporting of surrogate end-points do not allow conclusions to be drawn regarding the relative effectiveness of IMRT compared with 3D-CRT.”

Medicare and Representative Private Insurer Coverage Policies

There is no Medicare national coverage determination for IMRT; local carriers universally cover it as a form of conformal radiation therapy. Initial Medicare coverage began in 2000 and IMRT

was given a new CPT code and a reimbursement at approximately \$42,000 vs. \$10,000 for 3DCRT. All national health plans whose medical policies were reviewed cover IMRT for localized prostate cancer, most stipulating coverage only when dose escalation > 75Gy is required.

Summary of ICER Literature Review on Comparative Clinical Effectiveness

- Several randomized controlled trials provide consistent evidence that dose escalation to 75-80 Gy, whether provided by 3D-CRT or IMRT, provides superior biochemical failure-free survival compared to conventional doses of approximately 70-72 Gy. There are no data supporting superior biochemical outcomes at radiation doses above 81 Gy.
- The literature on comparative rates of toxicity has serious methodological weaknesses. There are no prospective randomized trials or cohort trials, and the case series that exist are hampered by the lack of contemporaneous cohorts and/or by a failure to describe the selection process by which patients were assigned to IMRT vs. 3D-CRT. Published case series demonstrate consistent findings of a reduced rate of GI toxicity for IMRT at radiation doses from approximately 75-80 Gy. Data on GU toxicity have not shown superiority of IMRT over 3D-CRT, nor do the existing data suggest that IMRT provides a lower risk of erectile dysfunction.
- The literature suggests that the risk of GI toxicity is approximately 14% with 3D-CRT and 4% with IMRT. Thus, the number of patients needed to treat to prevent one case of moderate-severe proctitis is 10, and for every 100 patients treated with IMRT instead of 3D-CRT, 10 cases of GI toxicity would be expected to be prevented.

Summary of Economic Model Structure and Content

A cost-effectiveness analysis was undertaken to determine the incremental cost-effectiveness of IMRT vs. 3D-CRT. We limited our analysis to considerations of comparative effects at the dosage range most commonly used for localized prostate cancer, 75-80 Gy. For the model we assumed that IMRT and 3D-CRT have similar biochemical relapse-free survival and overall survival when delivered within this range.

Based on the input from the scoping committee, we focused on late toxicities of treatment that met or exceeded grade 2 in the Radiation Therapy Oncology Group's morbidity grading scale. The risk of toxicities from IMRT and 3D-CRT were established from a systematic review of the literature and informed by clinician expert input. Utilization and cost data for radiotherapy treatments and for the additional care needed for patients with toxicities came from the literature, clinician interviews, and data from the Centers of Medicare & Medicaid Services. The model assumes that patients with GI toxicity are first treated with a 6 month course of an anti-inflammatory enema, which effectively controls bleeding in 70% of patients. The remaining 30% of patients are assumed to undergo an average of three sigmoidoscopy procedures with laser coagulation for intractable bleeding, followed by an additional 6 month course of enemas.

**Summary of Findings of Economic Model:
IMRT vs. 3D-CRT for localized prostate cancer**

- Cost of IMRT = \$42,450
- Cost of 3D-CRT = \$10,900
- The cost per case of proctitis prevented = \$313,000
- The cost per quality-adjusted life-year (QALY) = \$706,000
- The cost of IMRT to achieve a cost/QALY of \$150,000 = \$19,100
- The cost of IMRT to achieve a cost/QALY of \$100,000 = \$16,900
- Variation in cost-effectiveness by risk of prior probability of proctitis from 3D-CRT:
 - If patient risk = 35%, cost/QALY = \$279,000
 - If patient risk = 75%, cost/QALY = \$117,000
 - If patient risk = 98%, cost/QALY = \$96,000

Evidence Review Group Deliberation

The ERG deliberation raised several important issues regarding the evidence provided by the ICER review. First, comments were made expressing the view that localized prostate cancer is a condition for which there are multiple treatment options, including watchful waiting, and that therefore evidence for new treatment options, particularly evidence on harms, should be scrutinized very carefully. There was also concern expressed that assumptions about the effectiveness of IMRT had gone unexplored. Specifically, concern was raised regarding the likelihood of significant variability in the skill and proficiency of community radiation oncologists and other practitioners now using IMRT. None of the published data come from studies outside top academic centers, and since IMRT requires sophisticated planning and delivery systems, the outcomes in community practice may fall below that shown in the literature. A second concern raised was that the more highly focused IMRT treatment may in fact miss unrecognized cancer foci outside the target zone in the prostate, and that longer-term data are needed to confirm that the effectiveness of IMRT is comparable to 3D-CRT.

The discussion of the ERG was dominated by consternation with the lack of RCT evidence and with the relative price set for IMRT reimbursement by Medicare in 2000. There was extensive discussion of the possible biases affecting the many case series studies that form the body of evidence on IMRT. On one hand, case series were viewed as very low quality evidence, quite susceptible to selection bias, time bias, and other factors that make interpretation of case series data difficult. In contrast, it was pointed out that case series can provide high confidence in outcomes if the findings are strikingly similar across different institutions implementing a new method in different years; if in each case series all patients arriving at the institution with the condition are switched all at once from 100% treatment with a previous method to 100% treatment with the new method; and if there are no other secular changes in treatment that might affect the incidence of harms or benefits.

In the end, the ERG was uneasy according high confidence to the IMRT data, expressing the opinion that there were still too many doubts about the internal validity of the case series data to warrant more than limited confidence in the net health benefit.

In discussing the balance of harms and benefits, the ERG noted that the sole distinction between the two methods was the possible reduction in harms offered by IMRT. Much time was spent debating whether the clinical literature and the economic model accurately captured the importance of proctitis. Some members of the ERG felt that proctitis was a greater and broader burden on quality of life than captured by our utility estimate. They noted that proctitis is more than just bleeding and urgency, and suggested we perform a sensitivity analysis on the utility of proctitis. This sensitivity analysis was performed after the ERG meeting and revealed that even if the impact of the disutility of proctitis is twice as much as obtained from the patient sample, the cost per quality adjusted life-year would still be \$343,400.

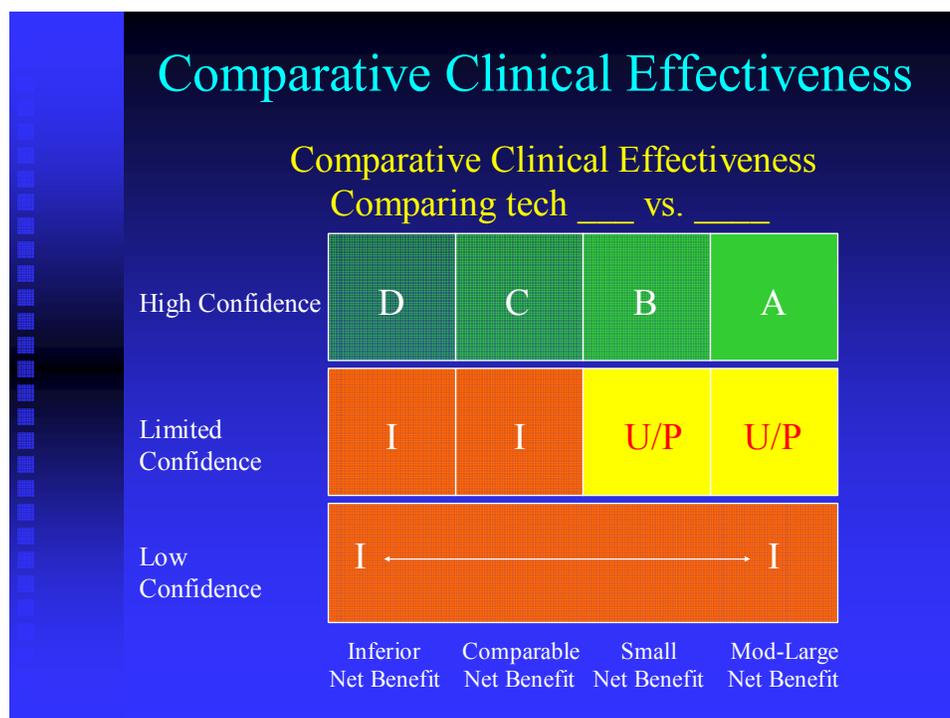
Some members of the ERG believe that, even if one accepts that IMRT reduces the risk of moderate-severe proctitis from 14-16% to 2-4%, this difference is not significant enough to warrant IMRT being judged more than comparable to 3D-CRT. Further discussion, however, led all members of the ERG to agree that the net health benefit rating for IMRT should be “incremental,” denoting a small net health benefit.

The discussion centering on the assignment of ICER evidence ratings revealed a strong majority of the ERG believed that there was only limited confidence in a small net health benefit for IMRT. One member of the ERG believed that IMRT’s comparative clinical effectiveness should be rated as “Insufficient” due to the lack of high quality data. The ERG was unanimous in judging the comparative value of IMRT as “low” on the basis of the high incremental cost-effectiveness ratio and the high cost of preventing a single case of proctitis. Although the economic model showed that the cost/QALY was \$117,000 for patients with a prior probability of proctitis of >75%, the clinical experts admitted that research had not been done to provide an evidence-based approach for identifying these patients.

ICER Integrated Evidence Rating™

Background

The ICER Integrated Evidence Rating™ combines a rating for comparative clinical effectiveness and a rating for comparative value. The clinical effectiveness rating arises from a joint judgment of the level of confidence provided by the body of evidence and the magnitude of the net health benefit -- the overall balance between benefits and harms. This method for rating the clinical effectiveness is modeled on the “Evidence- Based Medicine (EBM) matrix” developed by a multi-stakeholder group convened by America’s Health Insurance Plans. This matrix is depicted below, and further details are available at the ICER website:



A = “Superior”

B = “Incremental”

C = “Comparable”

D = “Inferior”

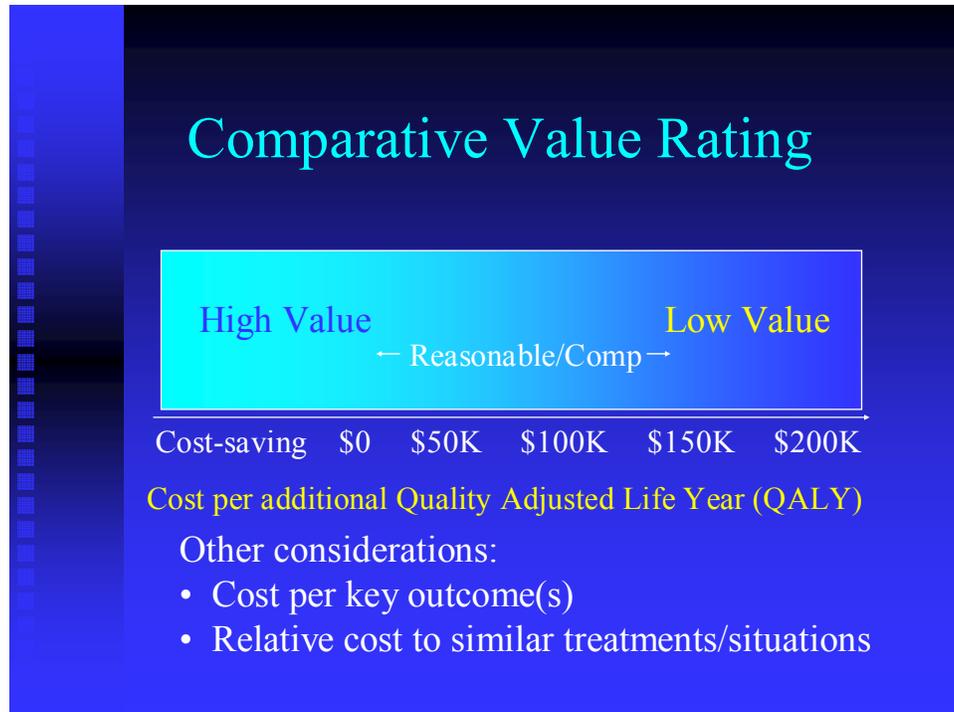
U/P = “Unproven but Potential” comparative clinical effectiveness.

This category is meant to reflect technologies with the following evidentiary characteristics:

- 1) Evidence of moderate quality and consistency suggesting a moderate-large net health benefit.
- 2) Limitations to the evidence are significant enough to provide a reasonable chance that further research would reveal that the technology provides a comparable or even inferior net health benefit.

I = The evidence is “Insufficient” to provide confidence that the net health benefit of the technology is not inferior.

The ICER rating for comparative value arises from a judgment largely based on the incremental cost-effectiveness of the technology being appraised. There are three categories of value: high, reasonable or comparable, and low. These categories are separated by loose boundaries established by health care researchers and policy makers.



ICER Integrated Evidence Ratings combine the ratings given for comparative clinical effectiveness and comparative value. The overall purpose of these ratings is to highlight the separate considerations that go into each element but to integrate them for the purposes of conveying that clinical benefits provided by technologies come at varying relative values based on their cost and their impact on the outcomes of care and the health care system. Further details on this methodology can be found at the ICER website.

ICER Integrated Evidence Rating™: IMRT vs. 3D-CRT

The Comparative Clinical Effectiveness of IMRT vs. 3D-CRT for localized prostate cancer is rated as:

- U/P --- Unproven with potential for small net health benefit.

The Comparative Value of IMRT vs. 3D-CRT for localized prostate cancer is rated as:

- c --- Low

The Integrated Evidence Rating = Uc

ICER Integrated Evidence Rating™
IMRT vs. 3D-CRT Rx 75-80 Gy

Comparative Clinical Effectiveness

Superior A	Aa	Ab	Ac
Incremental B	Ba	Bb	Bc
Comparable C	Ca	Cb	Cc
Unproven/Pot U/P	Ua	Ub	IMRT = Uc
Insufficient I	I	I	I
Comparative Value	a High	b Reasonable/ Comparable	c Low

Evidence Review Group members

The Evidence Review Group (ERG) is an independent group brought together by ICER and composed of academic experts, patients, clinicians, epidemiologists, ethicists, and medical policy representatives of stakeholder groups including health plans and manufacturers.

The purpose of the ERG is to guide and help interpret the entire appraisal process. Members of the ERG are first convened to function as a “scoping committee” for the appraisal. During this phase the key questions for the appraisal are outlined, including elements such as the appropriate comparator technologies, patient outcomes of interest, patient subpopulations for which clinical and cost-effectiveness may vary systematically, time horizon for outcomes, and key aspects of the existing data that must be taken into account during the appraisal. The ERG may be divided into sub-committees that advise the ICER appraisal team at the mid-point of the appraisal on the early findings and challenges encountered.

At the final ERG meeting, members are asked to declare any interests in the technology or its comparator(s). The ERG meeting allows for in-depth deliberation on the findings of the ICER appraisal document and provides an opportunity for comment on the determination of the ICER integrated evidence rating. The minutes of each ERG meeting, including the names of the members and their declarations of interests, will be posted on the ICER website as soon as that website is established.

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INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

APPRAISAL OVERVIEW

INTENSITY MODULATED RADIATION THERAPY (IMRT) FOR LOCALIZED PROSTATE CANCER

The overview is written by members of ICER's research team. It represents the information received by the Evidence Review Group members prior to the committee meeting. The overview summarizes the evidence and views that have been considered by ICER and highlights key issues and uncertainties.

Final Scope

Rationale for the Appraisal

IMRT is a form of external beam radiation therapy developed in the mid-late 1990s that uses multiple beam angles and non-uniform beam intensities along with CT based computer planning to conform the radiation to the target organ in order to spare normal adjacent structures. IMRT thus has many similarities with three dimensional conformal radiation therapy (3D-CRT), itself an innovation of the early 1990s that uses CT imaging to construct 3D images to help maintain full dose to the target organ while decreasing the radiation dose to normal tissue. IMRT was initially conceived of as a specialized technique for use on rare tumors such as those that envelop the spinal cord, but the dissemination and use of IMRT accelerated greatly following Medicare approval in 2000 of reimbursement rates significantly higher than those for 3D-CRT. The most common use of IMRT today is for the primary treatment of localized prostate cancer, one of the most common of all cancers. The major treatment options for localized prostate cancer include radiation therapy such as IMRT and 3D-CRT, brachytherapy, surgery, and watchful waiting. Data to compare the long-term survival benefits of these options are limited, and thus the choice of a treatment option for many patients is based on considerations of the potential short and long-term side effects of different treatment options. Among radiation oncologists, advocates of IMRT say that research has demonstrated its superiority to 3D-CRT in reducing the risk of significant toxicities while allowing higher doses of radiation to be safely delivered. Others, however, have highlighted continued gaps in the evidence supporting the safety and effectiveness of IMRT, and suggest that there are unknown risks associated with the method of delivery of radiation by IMRT compared to 3D-CRT. IMRT is now used for localized prostate cancer by a substantial majority of practicing radiation oncologists; the technology is widely covered by public and private insurers at a cost approximately four times that of 3D-CRT.

Given the availability of several treatment options for patients with localized prostate cancer, the uncertainty over clinical risks and benefits, and the substantial difference in treatment costs, patients, clinicians, and payers will benefit from a formal appraisal of the comparative clinical effectiveness and comparative value of IMRT vs. 3D-CRT.

Objective:

To appraise the comparative clinical effectiveness and comparative value of IMRT versus 3D-CRT in the treatment of localized prostate cancer.

Key questions:

- 1) What are the effects of IMRT vs. 3D-CRT on survival, disease-free survival, incidence of adverse side effects, quality of life, and health care utilization and costs?
- 2) Based on these findings, what is the estimated cost per serious adverse event prevented and the cost per quality adjusted life-year gained for IMRT vs. 3D-CRT?
- 3) What are the key patient clinical characteristics that may influence the clinical and cost-effectiveness of IMRT compared to 3D-CRT?

Key considerations highlighted by scoping committee:

- 1) Interventions: Only localized treatment will be considered, i.e. whole pelvis radiation therapy and androgen deprivation therapy as they relate to IMRT and 3D-CRT will not be considered. In addition, different delivery techniques of IMRT, including variations on multileaf collimators and tomotherapy 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 immobilization strategies and techniques of image guidance integrated into treatment machines. All of the above strategies are not unique to IMRT and can also be adapted to 3D-CRT.
- 2) Clinical Outcomes: Patient input on the scoping committee indicated that acute, short-term toxicity was an anticipated and manageable facet of radiation treatment. They cared most about persistent side effects. Late moderate-to-severe (RTOG Grade ≥ 2) toxicities of the GI, GU, and sexual systems, therefore, were selected a priori as the key toxicity-related outcome measure for this assessment.
- 3) Costs: No special considerations about the nature of the costs of treatment or of the technology were identified by the scoping committee.
- 4) Professional considerations: Note was made that scrutiny of IMRT by CTAF has aroused great concern among some radiation oncologists and within their professional association. IMRT has been featured in the press as a lucrative procedure for physicians and questions have been raised about its rapid expansion and use.
- 5) Ethical considerations: There appear to be no specific ethical concerns. Prostate cancer is not specific to a vulnerable population; although it is a cancer, IMRT is not a “last-chance” type therapy; and the interpretation of patient utilities and modeling are not likely to present particular dilemmas.

1. Background

1.1 The Condition

Prostate cancer is the most common nondermatologic cancer in men. In 2006, approximately 230,000 new patients in the United States were diagnosed with prostate cancer and 27,000 men died of the disease. Every American man is estimated to have a 1 in 5 chance of developing prostate cancer at some time in his life, and as the population ages the number of new cases of prostate cancer is expected to grow substantially (Jemal, 2006).

The initial detection of most prostate cancers is made using either a digital rectal examination or a prostatic specific antigen (PSA) blood test. The diagnosis requires a biopsy of the prostate, usually performed by a needle under transrectal ultrasound guidance. A pathologist assigns a Gleason grade to the biopsy specimen based on the histologic appearance of the cancer cells, and a clinical stage is assigned based on the TNM 2002 classification scheme of the American Joint Committee on Cancer.

As a result of widespread PSA testing, most patients today are diagnosed with asymptomatic, clinically localized cancer. However, clinically localized disease encompasses a heterogeneous group of tumors which are subdivided into the following stages:

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 55 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 on-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

A combination of stage classification, Gleason score, and PSA level is widely used to help assess the risk of spread of microscopic tumor beyond the prostate, determine the risk of recurrence, and thus estimate the likelihood of success of local therapy. Several nomograms have been developed to help assess these risks (Partin, 2001). Definitions of low, intermediate, and high risk disease have varied slightly across various approaches, but the most influential risk stratification algorithm, used by the National Comprehensive Cancer Network (NCCN), has been well-validated and widely published (D'Amico, 1999). The NCCN guidelines define 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.

New independent prognostic factors are being developed, and the next generation of nomograms will likely incorporate pretreatment and post-treatment variables to predict important clinical endpoints (NCCN, 2007). Yet the current risk categories are widely cited and used as a core element of physician decision-making and of discussions with patients of the options for the treatment of clinically localized prostate cancer.

1.2 Treatment Options

Although this appraisal focuses on radiation therapy options for local treatment, it should be emphasized that active surveillance is a reasonable strategy for many patients with prostate cancer. For example, one study demonstrated that the probability that a patient with a Gleason score of 2-4 (low risk by NCCN nomogram) will die of prostate cancer within 15 years is only 6 per 1000 person years. Even among men who have moderately differentiated disease (Gleason 7), this study found that a majority will die from competing medical conditions during a period of 15 to 20 years (Albertson, 2005). On the other hand, another long-term study of early-stage prostate cancer found that the mortality rate from prostate cancer was approximately 6-fold higher after 15 years of follow-up when compared with the first 5 years (Johansson, 2004). In addition, a recent randomized controlled trial of radical prostatectomy versus watchful waiting for patients with early-stage prostate cancer demonstrated an absolute risk reduction of all-cause mortality of 2 percent and 5 percent after 5 and 10 years, respectively (Bill-Axelson, 2005). There are two ongoing randomized trials evaluating active surveillance as one of the primary treatment options in men with PSA-diagnosed early-stage prostate cancer, but their results are not expected until after 2010. In the meantime, until better prognostic markers are developed, many patients and physicians will continue to prefer aggressive treatments for clinically localized disease at the time of diagnosis.

The most commonly-employed medical treatments for prostate cancer include:

- 1) surgery to remove the entire prostate gland and surrounding structures (radical prostatectomy)
- 2) external beam radiotherapy (EBRT)
- 3) interstitial radiotherapy (brachytherapy)
- 4) freezing the prostate (cryotherapy)
- 5) androgen suppression therapy (AST)

There is little high-quality data with which to compare the relative effectiveness of these various treatments. The data that do exist suggest that these interventions have comparable cure rates but quite different side-effect profiles (Jani, 2003). There is thus no single “gold standard”

approach, and patients and physicians face a difficult choice among this extensive menu of treatment options. In such a situation, guidelines, clinical opinion, and patient choice are guided strongly by relevant information on the known risks of side effects among different treatments. And it is in this vein that the distinctive features of IMRT have been most discussed.

2. The Technology and its Comparator(s)

IMRT is a form of EBRT developed in the mid-late 1990s that uses multiple beam angles and computed tomography (CT) based computer planning to conform the dose to the target organ as closely as possible in an attempt to spare normal adjacent structures. EBRT as a general approach has long been one of the mainstays of treatment of clinically localized prostate cancer, and in one form or another it is selected as the initial therapy for approximately 25% of all patients (Wilt, 2007). EBRT is noninvasive and has no surgical risks, so it may be offered to patients who for reasons of age, general health, or specific coexisting conditions might not tolerate prostatectomy well. The most common adverse effects from radiation therapy are due to the effects of the radiation on adjoining tissue of the gastrointestinal, genitourinary, and sexual organs. All toxicity effects are classified as acute (within 90 days of treatment) or late (occurring or beginning >90 days after treatment) (Cox, 1995). Early gastrointestinal symptoms include abdominal cramping, tenesmus, and urgency and frequency of defecation and are usually controlled with antidarrheal agents or topical anti-inflammatory preparations. Late gastrointestinal effects include urgency, frequency, and bleeding from the lining of the rectum, which may require laser coagulation. Strictures, ulceration, and perforation are rare. Moderate-to-severe acute genitourinary effects are caused by irritability of the bladder detrusor or urothelial inflammation, resulting in urgency, frequency, or dysuria. Late genitourinary effects include bladder-neck or urethral stricture, causing urgency, frequency, and sometimes acute retention. Erectile dysfunction is common and occurs as a result of the disruption of penile vasculature (Pisansky, 2006).

The incidence of rectal, urinary, and sexual toxicities has provided a barrier to the desire to increase radiation doses in hopes of improving local tumor control. 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. 3D-CRT was introduced in the early 1990s and quickly became accepted as the standard treatment for many tumors, like prostate cancer, whose proximity to normal organs increase the risk of toxicity from 2D techniques. With 3D-CRT, 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 (Khoo 2005).

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), which was developed in the late 1990s, uses computer software and hardware to vary the shape

and intensity of external-beam radiation delivered to different parts of the treatment area. IMRT relies on inverse treatment planning using digitally reconstructed radiographs generated from 3-dimensional images (e.g. CT scans), and either modulates intensity of radiation beams to achieve non-uniform cross-sections, or spirally delivers a single narrow beam (tomotherapy), to target highly conformal radiation at tumors. Unlike 3D-CRT, which delivers radiation at a constant dose to a defined field, IMRT delivers non-uniform beam intensities that are consecutively cross firing and converging at the treatment target so that the dose is maximal at the target and reduced in the surrounding tissue.

2.1 Potential advantages of IMRT

The basic premise underlying the potential advantages of IMRT over 3D-CRT is that sculpting the radiation to the target volume of the cancer 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. Based on these two potential advantages there arise two specific roles for IMRT (Esiashvili et al., 2004):

- IMRT as an alternative to 3D-CRT for total doses from 75 to 79 Gray units (Gy). At this radiation dose the incremental value of IMRT primarily relates to a potential decrease in toxicities.

- IMRT as the only way to deliver total doses of 80 Gy and above with acceptably low rates of toxicity.

At these doses (“ultra high dose”) the incremental value of IMRT is postulated to relate to its ability to keep the risk of toxicities within reasonable ranges while improving chances of cancer cure.

The clinical goal of increasing radiation doses for localized prostate cancer is supported by the results of randomized clinical trials using biochemical failure as a surrogate outcome. For example, Pollack and colleagues compared the outcomes of 70 Gy delivered via 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 were 64% and 70%, respectively. The dose escalation preferentially benefited those with a PSA of 10 or greater. In another randomized controlled trial, Zietman compared 70 Gy vs. 79 Gy in 393 patients with Stage T1b through T2b prostate cancer; patients were followed for 5 years (Zietman 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. In contrast to the Pollack study, both patients with high and low risk disease benefited from dose escalation. 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 via 3D-CRT (Peeters 2006). 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.

None of these studies reported improvements in disease-specific or overall survival, but, taken together, their results have been interpreted to suggest that dose escalation to 75-80 Gy is associated with improved patient outcomes, particularly in men with intermediate and high risk

clinically localized prostate cancer. As a result, the 2007 NCCN guidelines state that whereas a standard dose of 70-75 Gy remains appropriate for patients with low-risk cancers, intermediate-risk and high-risk patients should receive doses between 75 and 80 Gy.

2.2 Potential disadvantages of IMRT

Despite the general enthusiasm for IMRT expressed in the majority of published articles, there are few long-term data assessing risks of IMRT, and not a single prospective simultaneous cohort or randomized controlled trial evaluating IMRT to 3D-CRT. The literature also describes several potential disadvantages to IMRT. IMRT methods to plan and deliver radiation therapy are not uniform. Many concerns about the safety and effectiveness of IMRT still exist, including increased machine head leakage through multileaf collimators and the spread of low-dose radiation to normal tissue, potentially increasing the risk of second malignancies; decreased dose rate and increased dose heterogeneity within targets, with unclear radiobiologic consequences; and steep dose gradients around targets that can move during and between treatments, potentially compromising target coverage and tumor control (Mell, 2005; Hall, 2003; Esiashvili, 2004). Some of these concerns are noted by the Guidelines for the Use of IMRT in Clinical Trials developed by the National Cancer Institute (NCI, 2007):

- A larger volume of normal tissue is exposed to low doses of radiation. This “whole-body leakage” may increase the risk of secondary malignancy, especially in light of the trend to catch prostate cancer earlier and in younger men.
- The high degree of conformation with IMRT may lead to geographic misses of the disease (cold spots) or to hot spots in unexpected locations.
- Set-up error or patient movement could lead to an inappropriately high dose delivered to normal tissue.

Risk of Secondary Malignancies

Among the potential disadvantages of IMRT, much discussion has focused on the risk of secondary malignancy. Several authors have noted this possibility, and one planning study that compared the radiation dose to the bone marrow of patients undergoing treatment for prostate cancer with IMRT vs 3D-CRT found that although IMRT increases the dose of radiation outside the treatment field and therefore could theoretically lead to an increase in radiation induced leukemias that occur earlier than solid tumors (Gershkevitch, 2005). 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 (Kry, 2005). Both factors may lead to an increase in second cancers. Kry and colleagues calculated the risk of fatal second malignancies for 6 different IMRT approaches. 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 (Kry, 2005). At least one planning study has found that IMRT can produce lower integral doses within the irradiated volume compared to 3D-CRT, with a commensurate decrease in rectal, bladder and bone doses that could translate to a lower risk of induced malignancies (Della Bianca, 2002). Although younger men more typically elect prostatectomy, while older men and those with comorbidities select EBRT, suggesting that an increased risk of a second malignancy may not be a great concern for those with a limited baseline life expectancy, 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.

2.3 Current penetration and use of IMRT

Use of IMRT in the clinical community has been expanding rapidly since the decision by the Centers for Medicare and Medicaid Services in 2000 to increase reimbursement rates for IMRT under the pass-through provisions of Medicare's Outpatient Prospective Payment System to four times the rate for conventional therapy. A 2004 survey of practicing radiation oncologists in the United States found that the proportion of respondents who used IMRT had risen to 73% compared with the figure of 32% percent found in the same survey in 2002 (Mell, et al., 2005). Among clinicians who used IMRT in 2004, 61% of academically-based clinicians used it for genitourinary (GU) cancers, whereas 93% of clinicians using IMRT in private practice used it for GU cancers. Major reasons cited for IMRT adoption were permitting normal tissue sparing (88%), dose escalation (85%), and economic competition (62%). Ninety-one percent of nonusers planned to adopt IMRT in the future.

3. Clinical Guidelines

National Comprehensive Cancer Network (NCCN): For patients with expected survival of more than 10 years, the current guidelines suggest:

- Low risk: expectant management or radical prostatectomy or radiation therapy (3D-CRT or brachytherapy), and
- Intermediate risk: radical prostatectomy or radiation therapy (3D-CRT with or without brachytherapy).
- High risk: hormone therapy and 3D-CRT or radical prostatectomy with lymph node removal.

The NCCN guidelines say IMRT may be used instead of 3D-CRT and do not discuss relative benefits and risks between the two technologies. As noted earlier, the NCCN guidelines state that “a standard dose of 70-75 Gy remains appropriate for patients with low-risk cancers. However, intermediate-risk and high-risk patients should receive doses between 75 and 80 Gy. Patients with high-risk cancers are also candidates for pelvic lymph node irradiation and the addition of neoadjuvant with or without adjuvant androgen deprivation therapy” (NCCN, 2007).

National Cancer Institute (NCI): 2005 guidelines from the NCI on the use of IMRT in clinical trials summarize the current state of the evidence supporting IMRT. The guidelines state that “IMRT is still a nascent technology.... 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.” (NCI, 2007)

American Society for Therapeutic Radiation and Oncology (ASTRO): ASTRO has formally concluded that “IMRT represents the preferred method currently available for the treatment of localized prostate cancer with external beam radiation therapy (EBRT).” (ASTRO, 2005).

American College of Radiology (ACR): The ACR has a practice guideline for IMRT that declares it effective while not addressing clinical indications or patient selection (ACR, 2003).

4. Previous Systematic Reviews/Tech Assessments

- Blue Cross Blue Shield Association Technology Evaluation Center (TEC)
The BCBSA TEC reviewed IMRT for cancer of the breast and lung in 2005 and concluded that available data were insufficient to determine whether IMRT is superior to 3D-CRT for improving health outcomes. TEC has not reviewed IMRT for prostate cancer.
- National Institute for Health and Clinical Excellence (NICE)
NICE has not reviewed this topic.
- Agency for Healthcare Quality and Research (AHRQ)
AHRQ is in the final stages of completing a technology assessment comparing treatments for early localized prostate cancer. The draft report does not distinguish IMRT from 3D-CRT among treatment options.
- California Technology Assessment Forum (CTAF)
CTAF evaluated IMRT for localized prostate cancer, producing a draft assessment in 2005. The assessment found that IMRT did not meet technology assessment criteria demonstrating that it improves net health outcomes. Negative response from the clinical community led CTAF to table its assessment. A roundtable symposium on IMRT for prostate cancer was held in January, 2007 but CTAF decided not to issue a formal decision. The summary of their symposium is available at <http://www.ctaf.org/content/calendar/detail/654>
- Canadian Agency for Drugs and Technologies in Health (CADTH)
CADTH has not reviewed this topic.
- National Coordinating Center for Health Technology Assessment (NCCHTA)
The NCCHTA in England produced a systematic review in 2003 of the clinical and cost-effectiveness of new and emerging treatments for early localized prostate cancer. Their work considered IMRT an advanced form of 3D-CRT and concluded that “the quality and paucity of evidence and the reliance on the reporting of surrogate end-points do not allow conclusions to be drawn regarding the relative effectiveness of IMRT compared with 3D-CRT.” Their report is available at <http://www.ncchta.org/execsumm/summ733.htm>

5. Medicare and Representative Private Insurer Coverage Policies

- There is no Medicare National Coverage Decision on IMRT. A review of Medicare Local Coverage Decisions (LCDs) suggests that IMRT is universally covered as a form of conformal radiation therapy. Many LCDs follow a format similar to that of the LCD from Empire Medicare Services (Empire Medicare Services, 2006). This LCD held that IMRT is “reasonable and necessary in instances where sparing the surrounding normal tissue is essential” and the patient meets at least one of several criteria regarding tumor shape, dose-limiting adjacent structures, etc., or “only IMRT techniques would decrease the probability

of grade 2 or grade 3 radiation toxicity as compared to conventional radiation in greater than 15 percent of radiated similar cases.” The LCD further notes that “IMRT is considered indicated for primary brain tumors, brain metastasis, prostate cancer, lung cancer, bladder cancer, pancreas cancer and upper abdominal sites, spinal cord tumors, head and neck cancer, adrenal tumors, pituitary tumors and situations in which extremely high precision is required.” In 2000, CMS increased reimbursement rates for IMRT to four times the rate for conventional therapy.

- Aetna (November 2006): IMRT is medically necessary for treatment of prostate carcinoma only when ultra high-dose radiation (dosage of 72 Gy) or more is planned.
- WellPoint (HealthLink) (June 2006): IMRT of the prostate is considered medically necessary in patients with non-metastatic prostate cancer for dose escalation >75Gy.
- United Healthcare (September 2006): IMRT is indicated when the following criteria are met: irregularly shaped tumors in close proximity to vital structures or sensitive normal tissue AND one of the following criteria: non-metastatic prostate cancer for dose escalation > 75 Gy or equivalent hypofractionated regimen.
- CIGNA Healthcare (November 2006): IMRT is covered as medically necessary for patients when there is reasonable concern about damage to surrounding tissue with the use of conventional EBRT or 3D-CRT.

6. Ongoing Clinical Trials

A number of clinical trials of IMRT in prostate cancer are underway as described in Appendix A (full descriptions are available at <http://clinicaltrials.gov>). Current or planned trials continue to examine the effectiveness of dose escalation using IMRT and/or 3D-CRT and different fractionation schedules, but no posted trial in the United States specifically randomizes patients in order to compare IMRT to 3D-CRT or other accepted alternative treatments. However, IMRT is in a phase III randomized clinical trial vs. 3D-CRT in Canada. That study began recruiting in 2005 and is not expected to be completed until 2014.

7. The Evidence

7.1 Systematic Literature Review

We searched MEDLINE from 1995 through December 2006 using the search terms “prostate cancer,” “intensity-modulated radiation therapy,” “IMRT,” “conformal radiation therapy,” and “3D-CRT.” We also searched the DARE database, www.clinicaltrials.gov, and contacted clinical experts to identify relevant references. Abstracts for all articles were read and articles reporting on results of clinical trials were retrieved along with review articles and systematic reviews. We did not search the non-English literature due to time and resource constraints. A

total of 62 articles were retrieved under the headings for IMRT, and 273 retrieved under headings for 3D-CRT. To restrict the review to the best available evidence, inclusion criteria based on the quality and applicability of studies were applied. Studies were eligible for abstraction if they reported clinical outcomes for 50 patients or more and had at least 50% of patients with localized prostate cancer. A flow diagram of the systematic review and a breakdown of articles by level of evidence is shown in Appendix A.

7.2 Comparative clinical effectiveness

7.2.1 Overview of literature

To date, no randomized study has been reported comparing the different available IMRT systems, IMRT vs. 3D-CRT, or IMRT vs. other treatment options for localized prostate cancer. Multiple studies have generated 3D-CRT and IMRT treatment plans from the same CT scans, then compared predicted dose distributions within the target and in adjacent organs at risk. Results of such planning studies show that IMRT improves upon 3D-CRT with respect to conformality to, and dose homogeneity within, the target. Dosimetry using stationary targets generally confirms these predictions (De Meerleer 2000, Kao 2004, Luxton 2001, Nutting 2000, Sethi 2003, Zelefsky 2000).

Clinical studies attempting to evaluate the difference in outcomes between IMRT and 3D-CRT are almost all retrospective case series describing the experiences of single institutions. Although some of these reports compare the outcomes of patients treated contemporaneously within the same institution, the absence of a randomized design makes the results difficult to interpret. The selection bias of patients for IMRT vs. 3D-CRT is not explored in the literature from institutions offering both treatments. Most of the case series in the literature involve patients from earlier years treated with 3D-CRT and patients in later years treated with IMRT. Often comparisons of stage, PSA, and other clinical factors are made to try to demonstrate that patients were clinically comparable across the years and that any difference in outcomes can therefore be ascribed to the treatment modality. There are two specific problems with this approach. First, patients in earlier years will have had, on average, longer follow-up periods within which to demonstrate late side effects, biasing the results in favor of the new treatment (Peschel, 2003). Second, there is evidence that Gleason scoring has changed over the years, and subtle changes in scoring may have caused an “upshift” in Gleason scores that will make the outcomes of patients in more recent years appear superior compared to patients with comparable Gleason scores in years gone by (Chism DB 2003).

The data on IMRT are also made difficult to interpret because of the many minor variations in how IMRT is delivered. Differences in patient positioning, the use of aids to stabilize the prostate, and variation in outcomes measurement (e.g. survey vs. chart review) present great difficulties in summarizing and comparing data across studies. For this reason no quantitative meta-analyses have been performed in the published literature. In summary, the scientific literature on the comparative clinical effectiveness of IMRT vs. 3D-CRT has important gaps, short follow-up, and all the inherent threats to internal validity of non-randomized data.

7.2.2 Disease-free and overall survival

There are no studies comparing outcomes of disease-free or overall survival between IMRT and 3D-CRT. However, as noted earlier, there is a body of evidence demonstrating improved biochemical outcomes with the application of higher radiation dose levels, a key element in the considerations for the advantages of IMRT.

Zelevsky, 2002

This is the largest study of IMRT in prostate cancer, a single institution case series of 772 patients (updated periodically in further publications) treated with IMRT between 1996 and 2001. A total of 698 patients were treated to 81 Gy and 74 patients were treated to 86.4 Gy. The median follow-up was 24 months. The three-year actuarial PSA relapse-free survival rates for low, intermediate, and high-risk patients were 92%, 86%, and 81%, respectively (no statistical test performed).

Pollack, 2002

In this prospective randomized controlled trial a conventional dose of 70 Gy was compared with a dose escalation to 78 Gy. The primary end point was freedom from failure (FFF). The FFF rates for the 70- and 78 Gy arms at 6 years were 64% and 70%, respectively ($p = 0.03$). Dose escalation to 78 Gy preferentially benefited those with a pretreatment PSA >10 ng/mL; the FFF rate was 62% for the 78 Gy arm vs. 43% for those who received 70 Gy ($p = 0.01$). For patients with a pretreatment PSA ≤ 10 ng/mL, no significant dose response was found, with an average 6-year FFF rate of about 75%. Although no difference occurred in overall survival, the freedom from distant metastasis rate was higher for those with PSA levels >10 ng/mL who were treated to 78 Gy (98% vs. 88% at 6 years, $p = 0.056$).

Kupelian, 2004

Nine institutions pooled data on patients with localized prostate cancer treated with > 60 Gy during the years 1994-95. The 5-year PSA disease-free survival for patients receiving <72 Gy was 63% vs. 69% for patients receiving >72 Gy. In this study the median follow-up duration in the >72 Gy group was essentially identical to the <72 Gy group because the study included a large number of patients treated consecutively during a narrow time range. Multivariate analyses controlling for the influence of pretreatment PSA levels, biopsy Gleason score, and clinical stage demonstrated that patients receiving higher radiation doses had improved PSA-disease free survival.

Zietman, 2005

Zietman's study was a prospective controlled trial of patients with early stage prostate cancer who were randomized to receive a dose of either 70.2 Gy or 79.2 Gy. The proportions of men free from biochemical failure at 5 years were 61.4% for conventional-dose and 80.4% for high-dose therapy ($p < 0.001$). In contrast to the findings of Pollack's 2002 study, the advantage to high-dose therapy was observed in both the low-risk and the higher-risk subgroups.

The study with the longest follow-up of patients treated with IMRT is a recent report from Memorial Sloan-Kettering Cancer Center (Zelevsky, 2006). In this report on the ongoing case series of patients at MSKCC treated with IMRT since 1996, the median followup was 7 years.

No increased rates of secondary malignancy were noted, but, as the authors note, follow-up beyond 10 years will be necessary to confirm these findings and establish the presence or absence of any deleterious effect of IMRT.

7.2.3 Toxicity

As noted earlier, there are no head-to-head trials of IMRT vs. 3D-CRT, and the few studies evaluating toxicities of treatment between the two approaches compare IMRT vs. 3D-CRT in non-contemporaneous case series at single institutions. Much of the comparison of toxicity rates between IMRT and 3D-CRT, therefore, must be made by comparing rates of toxicity found in more recent studies of IMRT alone with rates of toxicity from historical case series and dose escalation trials of 3D-CRT. The following table summarizes the evidence on toxicity. Individual key articles are discussed subsequently.

Table 1. Summary of data on toxicity of 3D-CRT and IMRT at comparable doses. Results are shown from highest rates of toxicity to lowest.

3D-CRT	<i>Late GI toxicity ≥ 2</i>	<i>Late GU toxicity ≥ 2</i>	<i>Impotence</i>
75-79 Gy	21% (Michalski, 2005) 19% (Shippy, 2007) 16% (Zelevsky, 1999) 16% (Skwarchuk, 2000) 14% (Zelevsky, 2001) 13% (Schultheiss, 1997) 12% (Jani, 2007) 11% (Peeters, 2005) 10% (Zelevsky, 2000) 10% (Kirichenko, 2007) 0% (D'Amico, 2006)	23% (Jani, 2007) 13% (Zelevsky, 2001) 13% (Shippy, 2007) 8% (Kirichenko, 2007)	39% (NCCHTA, 2003) 28% (D'Amico, 2004)
IMRT	<i>Late GI toxicity ≥ 2</i>	<i>Late GU toxicity ≥ 2</i>	<i>Impotence</i>
75-81 Gy	6% (Kirichenko, 2007) 6% (Jani, 2007) 4% (Zelevsky, 2002) 3% (Shippy, 2007) 2% (Zelevsky, 2006)	23% (Jani, 2007) 19% (Shippy, 2007) 15% (Zelevsky, 2002) 6% (Kirichenko, 2007)	49% (Zelevsky, 2006) 48% (Zelevsky, 2002)

Zelevsky, 2000

Zelevsky and colleagues at Memorial Sloan-Kettering Cancer Center have the most extensive published experience with IMRT outcomes. In a series of articles that continues to trace an expanding case series, their first article in 2000 reported on toxicities of 61 patients treated with 3D-CRT and 171 patients treated with IMRT, all to 81 Gy. 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. 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.

Zelevsky, 2001

The above study was followed by a larger case series of 1,100 patients treated with 3D-CRT or IMRT, with overlapping patients from the initial feasibility study. The case series runs from 1988 to 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 the NCCN nomogram. 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%).

Zelevsky, 2002

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 continued to include overlapping patients from the previous studies. In contrast to the previous report, however, all patients in this publication 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. 217 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 5 patients developed a urethral stricture requiring dilation. 11 patients (1.5%) developed Grade 2 rectal bleeding and four patients developed Grade 3 rectal toxicity requiring transfusions and/or cautery. Of the patients who were potent prior to treatment, 52% maintained their potency.

Zelevsky, 2006; Shippy, 2006

The most recent article from this group evaluates only 561 patients treated with IMRT to a dose of 81 Gy from 1996 to 2000. It is unclear why this later article has a different patient population than the earlier 2002 report. The 8-year actuarial likelihood of late grade 2 or greater rectal toxicity was 1.6%; the comparable likelihood of grade 2 or greater urinary toxicity was 15%; and the risk of erectile dysfunction was 49%. An abstract by Shippy based on patients from the same institution from 1988 to 2000 found a 10-year incidence of grade 2 or greater rectal toxicity of 3% for patients treated with IMRT as opposed to 19% for patients treated with 3D-CRT.

Jani, 2007

A case series report from the University of Chicago, this study evaluates the toxicity outcomes for 461 patients from 1998 to 2005, 355 treated with IMRT and 106 with 3D-CRT. Patient selection for one treatment vs. the other is not discussed. Jani's findings are consistent with Zelefsky's studies that document reduction of GI but not GU toxicity with the use of IMRT. The study claim to be the first-ever of the step-and-shoot mode of IMRT delivered in the supine position.

Kirichenko, 2006

This abstract from Fox Chase Cancer Center compared treatment-related morbidity between IMRT and 3D-CRT for 928 patients treated at that single institution from 1995-2004. The prescription dose for IMRT was 74-78 Gy, whereas the 3D-CRT patients received a median dose of 72 Gy. Patients were found to be well-matched for PSA, stage, clinical comorbidities, and other features. The 3-year actuarial risk for late Grade >2 GI toxicity was 6.2% vs. 10.4% for IMRT vs. 3D-CRT. Late GU toxicity was slightly increased in IMRT patients (8.4% vs. 5.7%), but this difference was not significant after *adjustment for clinical and treatment features*.

8. Summary

8.1 Health Benefits

The first element in the clinical rationale for IMRT is that dose escalation to at least 75-80 Gy provides the potential for superior long-term disease-free and overall survival for patients with localized prostate cancer. Although the literature is limited by methodological concerns, the articles from several randomized controlled trials do provide consistent evidence that dose escalation to this range provides superior biochemical failure-free survival, and in the absence of long-term outcomes this conclusion has created a strong clinical consensus that for patients with intermediate and high-risk localized prostate cancer, the radiation dose delivered should be at least 75-80 Gy. Zietman's 2005 study suggests that even low-risk patients may benefit from dose escalation to this level, but the Pollack 2002 data did not find this to be the case, and therefore consensus groups such as the NCCN have not stipulated that low-risk patients require treatment above conventional doses.

Whereas there are data from one institution that doses as high as 86.4 Gy may be delivered via IMRT with acute and late toxicity rates that do not differ substantially from lower doses, this experience is still quite limited, there are no data yet to support superior biochemical failure rates for 86 Gy vs. 81 Gy, and even current research at most institutions seems oriented toward other formats for IMRT (e.g. hypofractionation) rather than dose escalation beyond 81 Gy. Future research may suggest that biochemical outcomes are superior with "ultra high dose" radiotherapy, but for now the evidence does not exist to support this potential superiority for IMRT over 3D-CRT.

The second leg in the logic underpinning the potential advantage of IMRT is that it can provide escalated doses from 75-81 Gy with lower risks for moderate-severe toxicity when compared to 3D-CRT. On this question the methodological limitations of the literature are much more

serious. All the case series are hampered by the lack of contemporaneous cohorts and/or by a failure to describe the selection process, and attendant biases, by which patients were assigned to IMRT vs. 3D-CRT. Nevertheless, a view of the literature presented in Table 1 above indicates consistent findings across case series of a reduced rate of GI toxicity for IMRT at comparable radiation doses from approximately 75-80 Gy. The heterogeneity of IMRT approaches, of duration of follow-up, and of method of outcome measurement make it difficult to be precise in estimating the rates of GI toxicity following IMRT or 3D-CRT, but the case series with the largest cohorts and longest follow-ups suggest that rates of late moderate-severe GI toxicity is approximately 12-14% for 3D-CRT and 4% for IMRT.

Data on GU toxicity have not shown superiority of IMRT over 3D-CRT. Authors have suggested that this is because IMRT does not in fact produce a consistently lower overall dose to key structures at the neck of the urethra (Jani, 2007; Zelefsky, 2002). Rates of late moderate-severe GU toxicity are approximately 15% with either IMRT or 3D-CRT.

Evaluation of the effects of IMRT vs. 3D-CRT on sexual dysfunction is severely hampered by the lack of reliable data. Many patients with prostate cancer already have erectile dysfunction, and reporting of this outcome is not routinely done as part of many studies. The 2003 NCCHTA systematic review looked in depth at this issue and concluded that most reports showed a rate of new erectile dysfunction of approximately 36-39% (NCCHTA, 2003). However, individual studies have found rates from as low as 20% to as high as 75%, all limited by variations in measurement methods. Previous analyses found that the risk of erectile dysfunction with 3D-CRT was roughly similar to that with conventional radiotherapy (Wilder, 2000), and planning studies have concluded that IMRT exposes the penile bulb and adjacent structures to similar (Kao, 2004) or less (Sethi, 2003) total radiation than 3D-CRT, but any confirmation by clinical outcomes is lacking. Therefore it is impossible on the basis of the data to assign a higher or lower incidence of erectile dysfunction to IMRT vs. 3D-CRT at comparable radiation doses.

8.2 Potential Harms

The literature is silent and cannot help ascertain the risks or benefits of various competing methods for delivering IMRT. Among the competing approaches are dynamic multileaf collimator (MLC), “step and shoot,” tomotherapy, and IMRT arc therapy. In a recent review one clinical expert stated that “Despite the improved dose distribution associated with IMRT, its use is limited by treatment errors that can result from organ movement and random, systematic or set up errors.... The quality assurance procedures for and fundamental questions regarding IMRT are evolving....” (Roach, 2004).

Similarly, the long-term risks for secondary malignancy cannot be assessed with current data. Clearly, most clinicians in the field do not believe that IMRT poses significant additional risks of malignancy, but the theoretical concerns will remain important, particularly for patients with life expectancy > 15 years, until long-term data are available.

8.3 Summary of Findings on Key Outcomes

Among the key clinical outcomes evaluated, differences between IMRT and 3D-CRT at doses of 75-80 Gy were not found for survival, disease-free survival; nor were differences found for GU toxicity or sexual dysfunction. The sole key clinical outcome on which there was evidence for a difference was the rate of GI toxicity.

- Number needed to treat = 10
Assuming that the absolute risk of GI toxicity is 14% with 3D-CRT and 4% with IMRT, the number of patients needed to treat to prevent one case of moderate-severe proctitis is:

$$\text{NNT} = 1 / (.14 - .04) = 10$$

- Cases prevented per 100 patients treated = 10
If 100 patients were treated with 3D-CRT there would be 14 expected cases of moderate-severe proctitis. If 100 patients were treated with IMRT there would be 4 expected cases. Therefore, for every 100 patients treated with IMRT instead of 3D-CRT, 10 cases of GI toxicity would be expected to be prevented.
- Patient-level information:
“Your risk of having moderate-severe proctitis is approximately 3 in 20 if we use 3D-CRT; your risk drops to about 1 in 20 if we use IMRT.”

9. Comparative Clinical Effectiveness: Additional Issues for Consideration

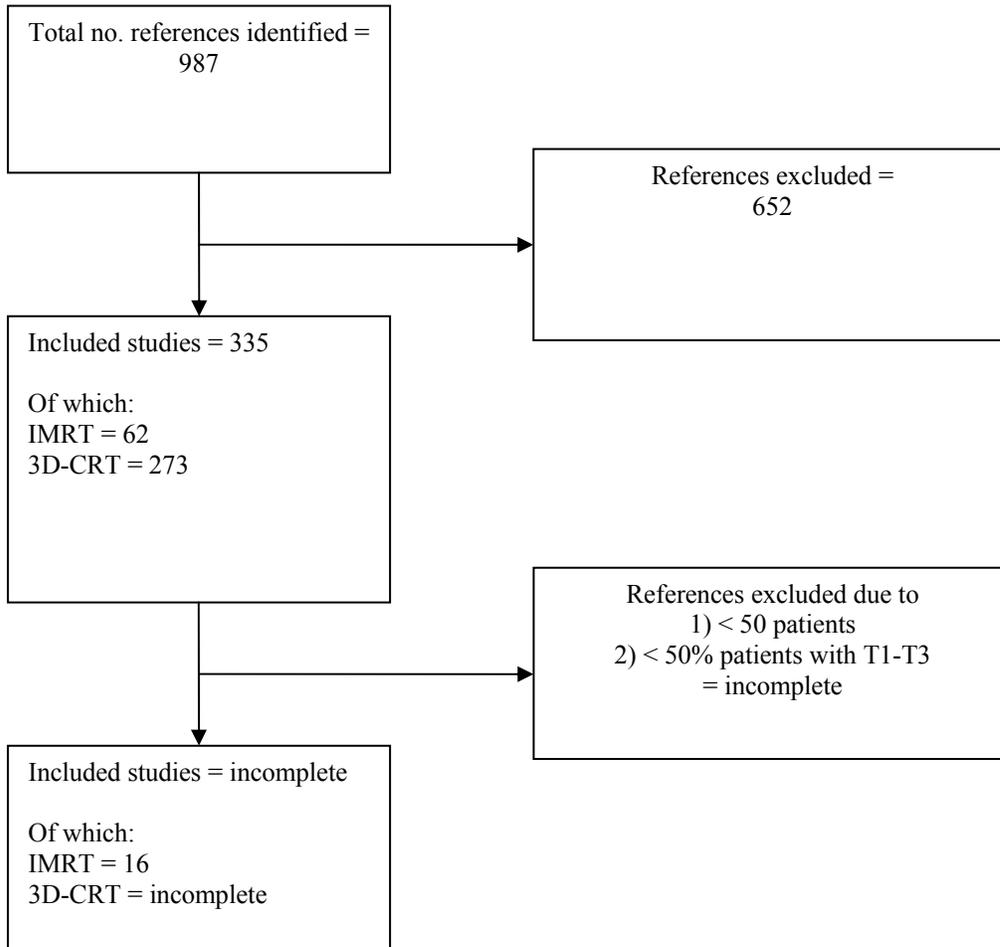
- Given the non-contemporaneous nature of most of the case series data comparing IMRT to 3D-CRT, are there secular improvements in techniques such as prostate stabilization that may skew the results in favor of IMRT?
- How much should the unknown long-term risk of secondary malignancy count in an assessment of the net health benefit of IMRT vs. 3D-CRT?
- Nearly all of the data on the outcomes of IMRT come from a handful of specialized academic centers. Does the complexity of IMRT require that we seriously examine the generalizeability of these findings to routine clinical practice in the community?
- Are there unique ways that IMRT is evolving to fit within other advances, e.g. hypofractionation or image-guided therapy that should be considered when comparing its net benefits to 3D-CRT?

Appendix A. Key research in progress

All information retrieved from www.clinicaltrials.gov, accessed 4/9/07.

Trial Sponsor	Design	Outcomes	Populations	Variables	Comments
Ottawa Health Research Institute (NCT00326638)	RCT	<ul style="list-style-type: none"> ▪ Late rectal toxicity from radiotherapy of the prostate 	Clinical stage T3-4	IMRT vs. 3D-CRT	Study start 2005; completion 2014
University Health Network, Toronto	Phase I Phase II	<ul style="list-style-type: none"> ▪ 			
Institute of Cancer Research, United Kingdom NCT00392535	RCT	<ul style="list-style-type: none"> ▪ Acute and late radiation-induced side effects ▪ Freedom from prostate cancer recurrence 	T1b-T3a, N0, M0	Conventional vs. hypofractionated high dose IMRT	
Fox Chase Cancer Center & NCI (NCT00062309)	RCT	<ul style="list-style-type: none"> ▪ Local and distant control ▪ Extent of disease eradication at 2 years ▪ Overall survival ▪ Quality of life 	Men with intermediate to high risk prostate cancer	Conventional IMRT vs. hypofractionated IMRT	
Barbara Ann Karmanos Cancer Institute & NCI (NCT00258466)	RCT	<ul style="list-style-type: none"> ▪ Chronic toxicity ▪ Disease free survival 	Favorable to intermediate prognosis, stage I-III adenocarcinoma of prostate	Neutron and photon radiotherapy vs. hypofractionated IMRT	
NCI multicenter (NCT00033631)	RCT	<ul style="list-style-type: none"> ▪ Survival at 5 years ▪ PSA failure ▪ Genitourinary and/or GI toxicity ▪ Erectile function ▪ Quality of life 	Low risk and some intermediate risk	Low dose vs. high dose	Treatment may be delivered by either 3D-CRT or IMRT, but delivery option is not a study variable
NCI	Phase I	<ul style="list-style-type: none"> ▪ Maximum tolerated dose of MRI-guided IMRT 	Not specified	Dose escalation	
Radiation Therapy Oncology Group & NCI (NCT00331773)	RCT	Disease free survival	Favorable risk stage II	Hypofractionated vs. conventionally fractionated delivery	Treatment may be delivered by either 3D-CRT or IMRT, but delivery option is not a study variable

Appendix B. Flow Diagram of Systematic Review Inclusion/Exclusion



We used previously published methods to determine the level of evidence, graded as follows:

- Systematic review
- Level 1 (randomized controlled trial)
- Level 2 (well-designed controlled trial without randomization)
- Level 3 (well-designed cohort or case-control analytical study)
- Level 4 (comparison between times or places with or without the intervention)
- Level 5 (opinions of respected authorities)

Of 16 included IMRT articles:
14 L5, 2 L4, 1 L1, 1 systematic review.

10. ECONOMIC MODEL OVERVIEW

10.1 OBJECTIVE

The objective of the economic model was to assess the incremental cost-effectiveness of using IMRT vs. 3D-CRT to treat patients with clinically localized prostate cancer. In accordance with the priority questions identified by the scoping committee, the economic model focuses on the differential toxicity rates of IMRT compared with 3D-CRT. The model does not include any potential benefit of IMRT on biochemical relapse rates for treated patients, nor does it include any potential increase in secondary malignancies.

10.2 METHODS

10.2.1 Overview of Model

Patients begin the model immediately prior to undergoing radiotherapy with IMRT or 3D-CRT. All patients incur costs related to their treatment modality. After treatment, patients are probabilistically categorized into eight categories, depending on the presence and type of treatment-related side effects they experience. The eight categories comprise all possible combinations of the presence or absence of late gastrointestinal, genitourinary, and sexual side effects, including a category for patients who experience no side effects.

After patients are categorized, outcomes related to costs and health effects are tallied. In particular, we quantified costs related to radiotherapy and treatment for side effects, utilities associated with different side effect profiles, life expectancy, and quality-adjusted life expectancy.

10.2.2 Type of Analysis

This study is a cost-effectiveness analysis (CEA). Incremental cost-effectiveness ratios are presented with costs in 2005 U.S. dollars and effectiveness in life-years and quality-adjusted life-years (QALYs). Intermediate outcomes (cases averted) are also reported.

10.2.3 Strategies

We evaluated two treatment strategies for patients with localized prostate carcinoma. They were: (A) Treatment with IMRT and (B) Treatment with high dose 3D-CRT. Both treatments were considered to be administered at a dose of 75 to 81 Gy.

10.2.4 Perspective

We followed most recommendations of the Panel on Cost-Effectiveness in Health and Medicine but adopted a payer perspective (Gold, 1996). We also used a 3% discount rate to bring costs and QALYs to present value, but present undiscounted values for some outcomes.

10.2.5 Target Population

We conducted our analysis for 69 year-old men with clinically localized prostate cancer and a low to intermediate risk of cancer recurrence. Patients at low-risk for recurrence typically have stage T1 to T2a lesions, Gleason scores between 2 and 6, and PSA levels less than 10 ng/mL. Patients at intermediate risk for recurrence were considered to have T2b to T2c lesions, Gleason scores exceeding 7, or PSA levels between 10 and 20 ng/mL. We assumed that both low- and high-risk patients would be treated with 75 to 81 Gy of radiation.

10.2.6 Time Horizon

A lifetime horizon was adopted to capture major healthcare costs and health effects in the main analysis.

10.2.7 Prevalence of Treatment-related Toxicities

We used the Radiation Therapy Oncology Group's morbidity grading scale to measure treatment-related toxicities, and only considered toxicities that met or exceeded grade 2 in severity (Lawton, 1991). We also only measured late toxicities, which are toxicities that occur at least 90 days after the end of radiotherapy, and did not consider the incidence of acute toxicities. Clinically, we tracked the side-effects rates in gastrointestinal, genitourinary, and sexual reproduction systems. These correspond with proctitis, incontinence, and impotence, respectively.

The estimate of the risk of toxicities from IMRT and 3D-CRT were based on the results of the systematic review of the literature and is anchored on the estimates from two large observational studies on outcomes following 3D-CRT and IMRT, both published by Zelefsky and colleagues (Zelefsky 2002; Zelefsky 2001). Though the data on IMRT reported most toxicity outcomes at a three year time point while the 3D-CRT data used a five year time point, toxicity prevalence rates were reported using Kaplan-Meier curves and these indicated that the incidence of new-onset late treatment-related toxicity was zero after two to three years. Hence, the late toxicity rates for the two treatments are likely to be comparable, despite their differing time points.

Urinary toxicity rates presented in the two studies differed, with the IMRT study reporting a 15% rate, and the 3D-CRT study reporting a 13% rate. There is, however, no clinical consensus that patients receiving either treatment are more or less likely to experience late urinary side effects. We therefore used a common value of 15% for the GU toxicity rate in all patients, irrespective of treatment type.

Impotence rates reported in the literature are also highly variable, with studies reporting figures as low as 28% and as high as 49% (D'Amico, 1999; Zelefsky, 2006). We used a common value of 50% for this side effect, irrespective of treatment type, based on our review of the literature and the opinions of clinical experts.

To estimate the likelihoods for combinations of side effects, we assumed independence between the overall incidence of each toxicity, and used equations of the form:

$$p_{GI} = p_{GI} \cdot p_{GU} \cdot p_{Sexual} + p_{GI} \cdot (1 - p_{GU}) \cdot p_{Sexual} + p_{GI} \cdot p_{GU} \cdot (1 - p_{Sexual}) + p_{GI} \cdot (1 - p_{GU}) \cdot (1 - p_{Sexual})$$

where p_{GI} , p_{GU} , and p_{Sexual} are the total probabilities of experiencing gastrointestinal, genitourinary, and sexual side effects, respectively. The four pieces on the right side of the equal sign correspond with the probabilities of experiencing all three side effects, GI and sexual side effects only, GI and GU side effects only, and GI side effects only, respectively. Similar equations were constructed for GU and sexual side effects.

A third Zelefsky study of 3D-CRT reported the median times to onset and resolution for GI and GU toxicities, and the median time to onset for sexual toxicity (Zelefsky, 1999). Patients typically began experiencing each of these toxicities between 12 and 24 months after receiving treatment, and resolution for GI and GU toxicities typically occurred 12 months after their onset. We applied these time points to our analysis and also assumed that patients with impotence were unable to attain erections for the remainder of their lives.

10.2.8 Biochemical and Overall Survival

We assumed that IMRT and 3D-CRT were associated with similar biochemical relapse-free survival and overall survival. The former was derived from an observational study and estimated at five years (Zelefsky, Wallner, et al, 1999). For overall survival, we assumed that the life expectancy for patients with clinically localized prostate cancer was similar to that of age-matched cohorts (Arias, 2006). Life expectancy estimates were also discounted to present value using an annuity factor:

$$A^T = [1/r - 1/(r \cdot (1+r)^T)]$$

where T is the number of years (rounded down to the nearest integer) the patient is expected to live, A^T is the annuity factor, and r is the discount rate. The annuity factor

was then added to the non-integer, decimal remainder of life expectancy after this decimal remainder was discounted to present value using T+1 time periods.

10.2.9 Health-related Quality of Life

Health state utilities for treatment-related toxicities were provided by Dr. Anirban Basu, who elicited these utilities from prostate cancer patients using time trade-off methods (Basu, 2007). The utility of a health state free of toxicity was estimated using age-matched, median EQ-5D results from a nationally representative sample (Sullivan, 2005). Patients who experienced more than one toxicity were assigned utilities that were a product of the utility of each toxicity. For example, a patient who experienced both gastrointestinal and sexual side effects would be ascribed a utility equal to:

$$U_{GI, GU} = U_{GI} * U_{GU}$$

where U_{GI} , U_{GU} , and $U_{GI, GU}$ are the health state utilities for patients experiencing GI, GU, and both side effects, respectively.

Patients were assumed to acquire their post-treatment health state and utility at the median time of onset reported by Zelefsky, and maintain them until the median time of resolution (Zelefsky, 1999). As stated previously, sexual dysfunction was assumed to be unremitting.

10.2.10 Direct Medical Costs

The cost of radiotherapy treatment was assumed to equal Medicare reimbursement and estimated using the 2005 Physician Fee Schedule from the Centers of Medicare & Medicaid Services (CMS, 2005). Current procedural terminology (CPT) codes and the corresponding number of units associated with each code were derived from a previous cost-effectiveness analysis conducted by Konski et al.(13) Total relative value units (RVUs), composed of work-related and facility-related pieces, and the 2005 national Medicare conversion factor of \$37.8975 per unit, were also used. Total RVUs also included technical and professional components, depending on the specific CPT code.

As reported by Konski et al., IMRT treatment costs were comprised of CPT codes for office consultation, treatment planning, immobilization and beam modifying devices, dosimetry calculations, port films, physics consultation, treatment management, treatment delivery, CT guidance for radiation administration, ultrasound guidance, IMRT-specific dose planning, and a special physics consultation and treatment procedure. 3D-CRT treatment costs were comprised of CPT codes for office consultation, treatment planning, conformal simulation, immobilization and beam modifying devices, dosimetry calculations, port films, treatment delivery, physics consultation, treatment management, simple simulation, isodose distribution, and CT guidance for radiation administration (Konski, 2006).

The cost of radiotherapy was therefore equal to the product of the total RVUs, number of units, and conversion factor. We did not consider the cost of other treatments that prostate cancer patients often receive, such as hormone and hormone agonist therapies. Because our analysis is incremental and we assume that both treatment modalities are equally efficacious, the incorporation of these costs would not impact incremental cost-effectiveness ratios.

Costs of treating treatment-related toxicities were derived from CPT codes, published studies, and structured interviews with clinicians. We assume that patients with GI toxicity are first treated with a 6 month course of an anti-inflammatory enema, which effectively controls bleeding in 70% of them. The remainder then undergo an average of three sigmoidoscopy procedures with ablation for intractable bleeding, followed by an additional 6 month course of enemas. We also include the cost of associated office visits.

Patients with GU toxicity are first treated with an anticholinergic agent for urinary frequency and urgency, which we assume to be universally effective for these conditions. Approximately 25% of patients also experience urethral stricture and require a bladder scan, complex uroflowmetry, and urethral dilation. Office visits are also included in the cost estimate.

Regarding sexual side effects, we estimated that only 30% of patients pursue treatment, and that the first line of therapy is Viagra for 97% of them. We also assume that these patients engage in sexual intercourse once per week. The remaining 3% of patients who do not take Viagra instead receive intracavernous injections for their impotence, and we again included the cost of necessary office visits.

11. RESULTS

11.1 Base Case Results

The incremental cost-effectiveness of IMRT compared to 3D-CRT in patients with clinically localized prostate cancer is \$706,000/QALY. The cost per case of proctitis averted associated with the use of IMRT is \$313,000.

11.2 Sensitivity and Threshold Analyses

We performed a sensitivity analysis on the cost of IMRT treatment. This cost would need to fall to \$19,100 and \$16,900 to achieve ICERs of \$150,000/QALY and \$100,000/QALY, respectively.

We also performed a sensitivity analysis on the risk of proctitis by holding the ratio of the GI toxicity rate of IMRT to 3D-CRT constant at 3.5, and varying the outcomes with 3D-

CRT. In the base case, this risk was 14%. Although no quantitative risk assessments were found in the literature, it is possible that clinicians can estimate higher risks for patients with certain underlying characteristics, such as history of inflammatory bowel disease or anticoagulation use. Results of a sensitivity analysis which assumed risk of GI toxicity at 35%, 70%, and 98% decreased the incremental cost-effectiveness ratio for IMRT to \$279,000/QALY, \$137,000/QALY, and \$96,000/QALY, respectively.

12. SUMMARY

Strong clinical evidence supports the notion that at comparable radiation doses IMRT effectively reduces the rates of proctitis in prostate cancer patients compared to conventional therapy with 3D-CRT. Our model suggests, however, that the incremental cost-effectiveness of IMRT is very high.

13. RECOMMENDATIONS FOR FUTURE RESEARCH

Limitations of current evidence

The body of evidence examining the comparative clinical effectiveness and comparative value of IMRT is limited to multiple case series, nearly all of which arise from single academic institutions. There are no prospective randomized trials of IMRT vs. 3D-CRT or any other modality of treatment for localized prostate cancer. There are no data on the outcomes of care for patients treated in more generalizable community settings. In addition, nearly all the literature to date on IMRT includes post-treatment outcome data of only several months' to several years' duration. Longer-term biological outcomes and overall survival data that would confirm the clinical effectiveness of IMRT are therefore lacking.

Examination of the relative harms of IMRT is also hampered by the low quality study design and short duration of existing trials. Data on side effects is also limited by varying methods of outcome measurement: studies use different approaches (chart review vs. patient survey); they use different scales to rate severity (RTOG vs. several others); and the breadth of outcomes reported (gastrointestinal, urinary, sexual dysfunction) is inconsistent across most studies. Outcome measurements rating the impact of various side effects on quality of life have usually lumped all side effects together, making it impossible to distinguish the true unique impact of each of the possible side effects of radiation treatment. Since IMRT appears to only reduce the risk of proctitis and not that of urinary or sexual side effects, the ability to measure the unique impact of gastrointestinal side effects is critical in judging the comparative effectiveness and value of this technology.

Evaluations of costs and cost-effectiveness are hampered by the lack of robust data on health care utilization by patients following radiation treatment, particularly the utilization of patients who require additional medical intervention due to side effects. Data were available only from a single paper and were buttressed by expert opinion for this appraisal, but further prospective data would greatly strengthen future analyses.

As noted in the appraisal document, the net health benefit and comparative value of IMRT would be substantially different were it possible to identify a priori patients with a particularly high prior probability of suffering proctitis from external beam radiation therapy. However, no clinical data exist to be able to create a decision guide to identify such patients.

Recommendations for future research

Practical and professional arguments have been presented that formal randomized controlled trials of IMRT are no longer possible given its penetration into practice and the logistical difficulties of randomization when a particular site may only have one treatment modality. Although randomized trials are underway in Canada and the UK, it would be possible to answer some of the most critical evidentiary weaknesses of existing literature with an observational research design. Based on the key evidentiary weaknesses revealed in this appraisal, and an assessment of which future research

findings would have the greatest impact on judgments of IMRT's comparative clinical effectiveness and value, ICER recommends the following studies be pursued:

1. 2-year prospective observational study of all patients undergoing radiation therapy treatments for localized prostate cancer across a broad spectrum of practice settings.
 - The 2-year horizon is recommended because it is believed that other ongoing studies will provide 5-year biochemical and overall survival information and that an additional study should therefore be as practical as possible in measuring outcomes that will affect decision-making regarding IMRT.
 - Patients undergoing IMRT, 3D-CRT, proton beam therapy, and brachytherapy should all be included in order to maximize the value of the data in comparing alternative radiation therapy approaches to localized prostate cancer.
 - This study should have broad inclusion criteria and should also include practitioners both inside and outside academic centers in order to enhance the generalizability of findings.
 - Patient clinical information should be gathered prior to initiation of therapy and should include standard measure of disease staging and histological severity as well as all potential risks for side effects (age, past history and current status of GI, GU, and sexual function, medications, co-morbidities).
 - Outcome measures should include: biological measures of disease; clinical recurrence; disease-specific and all-cause mortality; RTOG-scale measured adverse effects; EQ-5D quality of life; measure of time lost from work and impact on productivity; and health care service utilization.

Table 1. IMRT model inputs.

Variable	Base case estimate	Source
Time points		
Rectal toxicity*		
Median time to onset, mo	12	(7)
Median time to resolution, mo	12	(7)
Urinary toxicity*		
Median time to onset, mo	12	(7)
Median time to resolution, mo	12	(7)
Sexual dysfunction*		
Median time to onset, mo	12	(7)
Median time to resolution, mo	Lifetime	(7)
Health risks		
IMRT treatment**		
Radiation dose (≤ 81 Gy)		
Rate of late rectal toxicity	0.04	(3)
Rate of late urinary toxicity	0.15	(3)
Rate of sexual dysfunction†	0.50	CEG
3D-CRT treatment‡		
Radiation dose (≥ 75.6 Gy, ≤ 81 Gy)		
Rate of late rectal toxicity	0.14	(4)
Rate of late urinary toxicity	0.15	(4), CEG
Rate of sexual dysfunction	0.50	CEG
Overall survival, yrs		
Life expectancy after IMRT	14.1	(9)
Life expectancy after 3D-CRT	14.1	(9)
Health state utilities		
No treatment-related toxicity	0.81	(11)
Late rectal toxicity	0.612	(10)
Late urinary toxicity	0.685	(10)
Sexual dysfunction	0.729	(10)
Costs, \$		
Treatment with IMRT	42450	(12)
Treatment with 3D-CRT	10900	(12)
Treatment for late rectal toxicity (expected cost per case)	2346	See text
Treatment for late urinary toxicity (expected cost per case)	954	See text
Treatment for sexual dysfunction (expected cost per case)	2113	See text

Abbreviation: CEG, clinician-expert guidance secondary to limited, methodologically poor data

*The median times to onset and resolution (except for resolution of sexual dysfunction) fall between 12 and 24 months, and a 12 month approximation was used for analytical tractability

**Cumulative incidence of IMRT toxicities measured at a three-year time point.

†Rate of impotence not reported separately for low-dose and high-dose patients, and is measured at a two-year time point.

‡Cumulative incidence of 3D-CRT toxicities measured at a five-year time point, but these values do not vary after three-years, based on Kaplan-Meier curves provided.

|| Rate of rectal toxicity estimated because of limitations due to author reporting, but is between 15% and 16% with certainty.

Abbreviations

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