INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

FINAL APPRAISAL DOCUMENT

INTENSITY MODULATED RADIATION THERAPY (IMRT)

FOR LOCALIZED PROSTATE CANCER

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Steven D. Pearson, MD, MSc
Joseph Ladapo, BA
Lisa Prosser, PhD

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 copared 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.

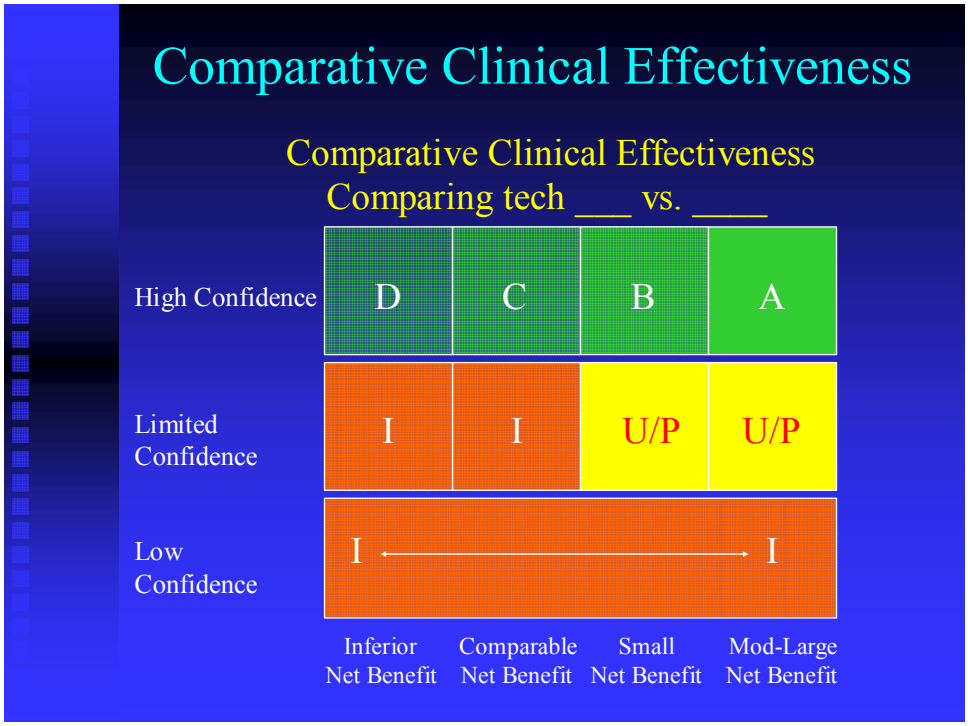
Some members of the ERG believe that, even if one accepts that IMRT reduces the risk of moderate-severe proctitis from 14-16% to 2-4%, this difference is not significant enough to warrant IMRT being judged more than comparable to 3D-CRT. Further discussion, however, led all members of the ERG to agree 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:

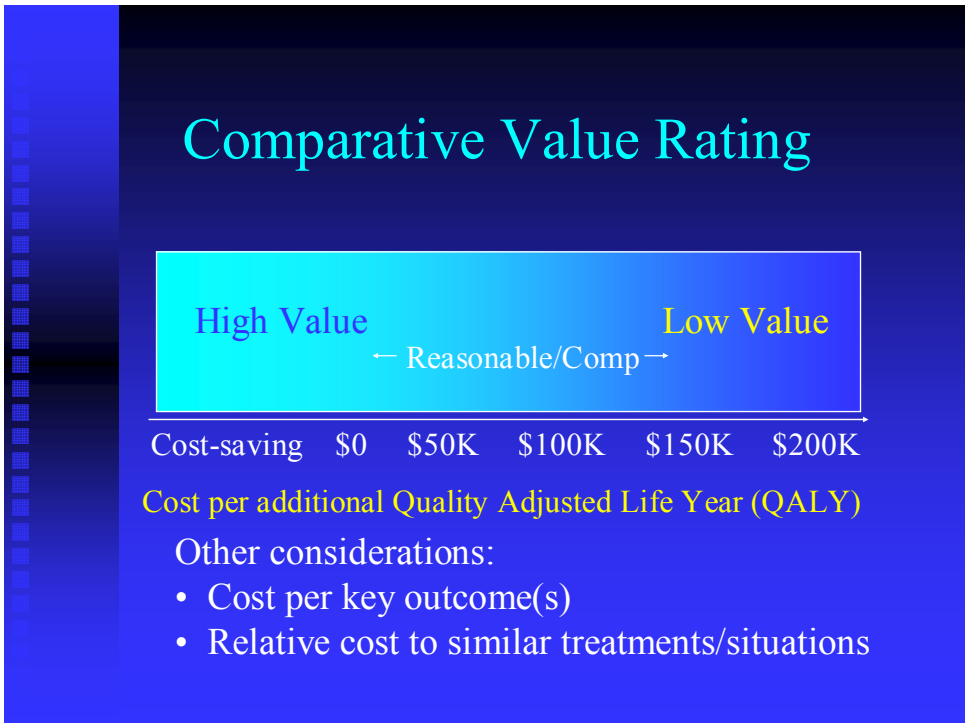


A = "Superior"
B = "Incremental"
C = "Comparable"
D = "Inferior"
U/P = "Unproven but Potential" comparative clinical effectiveness.
This category is meant to reflect technologies with the following evidentiary characteristics:

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

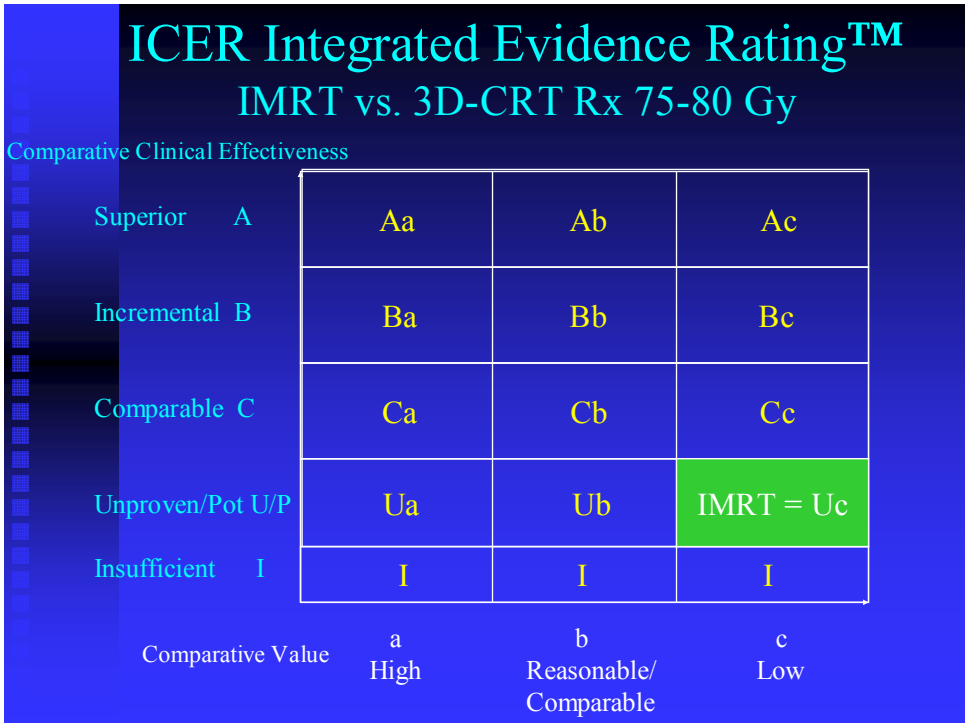
The Comparative Clinical Effectiveness of IMRT vs. 3D-CRT for localized prostate cancer is rated as:

- **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



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.

Jerry Avorn, MD
Professor of Medicine
Harvard Medical School
Chief, Pharmacoepidemiology & Pharmacoeconomics
Brigham & Women's Hospital

R. William Corwin, MD
Medical Director, Medical Management & Policy
Harvard Pilgrim Health Care

Chris Covington, MBA (patient)
Founder & Chairman,
Covington Associates

Kay Dickersin, PhD
Professor and Director, Center for Clinical Trials, Department of Epidemiology
Johns Hopkins School of Public Health
Baltimore, MD

Wendy Everett, ScD
President
New England Healthcare Institute

Theodore G. Ganiats, MD
Professor and Interim Chair
Department of Family & Preventive Medicine
Executive Director, Health Services Research Center
University of California San Diego

Louis L. Hochheiser, MD
Medical Director, Clinical Policy Development
Humana, Inc.

Jerome P. Kassirer, MD
Distinguished Professor and Vice Chair
Department of Medicine
Tufts University School of Medicine

Andre Konski, MD, MBA, MA
Clinical Research Director
Fox Chase Cancer Center
Philadelphia, PA

Robert E. Mechanic, MBA
Director
Health Industry Forum
Heller School of Social Policy and Management
Brandeis University

Richard Platt, MD
Professor and Chair
Department of Ambulatory Care & Prevention
Harvard Medical School and Harvard Pilgrim Health Care

James E. Sabin, MD
Director, Ethics Program
Harvard Pilgrim Health Care
Clinical Professor
Department of Ambulatory Care & Prevention and Psychiatry
Harvard Medical School

Martin G. Sanda, MD
Associate Professor of Surgery
Harvard Medical School
Beth Israel Deaconess Medical Center

Steven M. Teutsch, MD, MPH
Executive Director, U.S. Outcomes Research
Merck & Co., Inc

Sean Tunis, MD, MSc
Founding Director
Center for Medical Technology Policy
San Francisco, CA

Anthony L. Zietman, MD, MB., BS
Professor of Radiation Oncology
Harvard Medical School
Massachusetts General Hospital

Carmen Zullo (manufacturer)
Nuclear Product Specialist
Siemens Medical Solutions

