The Institute for Clinical and Economic Review (ICER)

Appraisal of IMRT vs. 3D-CRT
Purpose of the Day

- What is the structure and role of the Evidence Review Group?
  - Independent
  - Constitution
  - Review of Draft Assessment
  - Confirm/comment on ratings of comparative clinical effectiveness and value
Structure of the Day

- Policy and political background
- Introduction to ICER and purpose of today
- Introduction to IMRT
- Lunch
- Clinical Effectiveness
- Comparative Value
- Tying it all together
Pratts Healing Ointment
For Man and Beast

We both use it!
Innovation: The Challenges
Health Care Costs

- Today the US spends on health care $2,100,000,000,000
- 16% of GDP, $1 of every $7 spent
- If nothing changes, by 2030 health care will consumer $1 out of every $3 of GDP
Figure 1-7.
Total Federal Spending for Medicare and Medicaid Under Different Assumptions About Excess Cost Growth, 1966 to 2050
(Percentage of gross domestic product)

Source: Congressional Budget Office.
US Health Technology Assessment

- Poor coordination
- Weak legitimacy
- Limited usefulness
- Incomplete integration
Proposed Agency

- A new Comparative Effectiveness Research agency has been proposed in Congress
- The agency would provide information on the relative clinical (and cost) effectiveness of alternative health care interventions
  - Drugs, devices, diagnostics, procedures
- Funding at the level of $5 billion dollars
Goals of ICER

- Stimulate broader national policy to integrate value considerations into comparative effectiveness initiatives
- Test new methods for making technology assessments more accessible and actionable
- Integrate assessment of comparative clinical effectiveness with “comparative value”
ICER

- Blue Shield of California Foundation
- Collaborative academic model
- Pilot appraisals
  - IMRT for localized prostate cancer
  - Virtual colonoscopy
  - Pegfilgrastim
ICER Appraisal Process

- Topic selection
- Scoping committee
- Technology assessment
  - Clinical effectiveness
  - Comparative value
- Presentation to Evidence Review Group (ERG)
- Final Report with Integrated Evidence Rating
Integrated Evidence Rating

Comparative Clinical Effectiveness

- Superior A
- Incremental B
- Comparable C
- Pot/Unprov P/U
- Inadequate I

Comparative Value

- a: High
- b: Reasonable/Comparable
- c: Low
Comparative Clinical Effectiveness
Comparing tech ___ vs. _____

Good Confidence
- A
- B
- C
- D

Limited Confidence
- P/U

Low Confidence
- I

Inferior Net Benefit
Comparable Net Benefit
Small Net Benefit
Mod-Large Net Benefit
Integrated Evidence Rating

Comparative Clinical Effectiveness

Superior A
Incremental B
Comparable C
Pot/Unprov P/U
Inadequate I

Comparative Value
a High
b Reasonable/Comparable
c Low
Economic Evaluation

“... the comparative analysis of alternative courses of action in terms of both their costs and consequences.”

Drummond, Stoddart & Torrance, 1987
Weighing up costs and effects

<table>
<thead>
<tr>
<th>Cost ($)</th>
<th>Effect (QALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New treatment</td>
<td>High extra cost, Low QALY gain</td>
</tr>
<tr>
<td></td>
<td>Low extra cost, High QALY gain</td>
</tr>
<tr>
<td>New treatment</td>
<td>Win-win</td>
</tr>
<tr>
<td></td>
<td>Lose-lose</td>
</tr>
</tbody>
</table>

CE threshold
Comparative Value Rating

<table>
<thead>
<tr>
<th>Cost-saving</th>
<th>$0</th>
<th>$50K</th>
<th>$100K</th>
<th>$150K</th>
<th>$200K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost/QALY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

High Value  ↚ Reasonable/Comp ← Low Value

Other considerations:
- Cost per key outcome(s)
- Relative cost to similar treatments/situations
## Integrated Evidence Rating

### Comparative Clinical Effectiveness

<table>
<thead>
<tr>
<th>Equivalent</th>
<th>Comparative Value</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior</td>
<td>High</td>
<td>Aa</td>
<td>Ab</td>
<td>Ac</td>
</tr>
<tr>
<td>Incremental</td>
<td>Reasonable/Comparable</td>
<td>Ba</td>
<td>Bb</td>
<td>Bc</td>
</tr>
<tr>
<td>Comparable</td>
<td>Pot/Unprov P/U</td>
<td>Ca</td>
<td>Cb</td>
<td>Cc</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Inadequate</td>
<td>Pa</td>
<td>Pb</td>
<td>Pc</td>
</tr>
</tbody>
</table>

### Comparative Value

- a: High
- b: Reasonable/Comparable
- c: Low

Applications of ICER ratings

- Coverage decisions
- Value-based insurance design
- Reimbursement platforms
- Physician compensation
- Patient-clinician decision support tools
Purpose of the Day

- Review of Draft Assessment
- Comment on ratings of comparative clinical effectiveness and value
- NOT an NIH consensus committee
- NOT to make coverage recommendations
- Help us improve the ICER process
Appraisal of IMRT vs. 3D-CRT
Appraisal of IMRT

Scope

- Patient population(s)
- Comparator(s)
- Key questions
  - Differences in disease-free and overall survival
  - Differences in side effects → quality of life
  - Patient characteristics that most influence clinical and cost-effectiveness of IMRT
Background

- Localized prostate cancer
  - Classification
  - Treatment options
  - Importance of side effects
IMRT and 3D-CRT

- Origins

- Potential advantages of IMRT
  - Decrease in toxicity
  - Ability to deliver “ultra high” doses $>81$ with acceptably low toxicity

- Potential disadvantages of IMRT
  - “Cold spots” within the field
  - Increased risk of secondary malignancy
  - Inadequate quality assurance of methods of delivery
Clinical Guidelines

- **NCCN**
  - Low risk → 70-75 Gy
  - Intermediate risk → 75-80 Gy

- **NCI**

- **ASTRO**
  - IMRT is “preferred method” for Rx
Ongoing Research

- Dose escalation with IMRT and/or 3D-CRT
- Hypofractionation
- No randomized trials in US of 3D-CRT vs. IMRT
- Canadian phase III RTC begun 2005, completed in 2014
Coverage, Reimbursement, Use

- Medicare
- Private insurers
- Reimbursement: 4 x 3D-CRT = IMRT
- 2002-2004: 32%-73% penetration
  - 61% academic and 93% community clinicians using for GU cancer
  - 91% of non-users planned to adopt in near future
The Evidence

- Previous tech assessments
  - AHRQ, 2007
  - CTAF, 2005-2006
  - NCCHTA, 2003
  - TEC, NICE, CADTH: no review

- Systematic literature review
  - 62 IMRT articles
  - 283 3D-CRT articles
Key Findings

- **Disease-free survival**
  - Benefits to escalation to 75-81 Gy
  - No data yet on >81 Gy vs. 75-81 Gy

- **Potential harms**
  - No data on secondary malignancy

- **Differential risk of toxicity**
<table>
<thead>
<tr>
<th>3D-CRT</th>
<th><strong>Late GI toxicity ≥ 2</strong></th>
<th><strong>Late GU toxicity ≥ 2</strong></th>
<th><strong>Impotence</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>75-80 Gy</td>
<td>21% (Michalski, 2005) 19% (Shippy, 2007) 16% (Zelefsky, 1999) 16% (Skwarchuk, 2000) 14% (Zelefsky, 2001) 13% (Schultheiss, 1997) 12% (Jani, 2007) 11% (Peeters, 2005) 10% (Zelefsky, 2000) 10% (Kirichenko, 2007) 0% (D’Amico, 2006)</td>
<td>23% (Jani, 2007) 13% (Zelefsky, 2001) 13% (Shippy, 2007) 8% (Kirichenko, 2007)</td>
<td>39% (NCCHTA, 2003) 28% (D’Amico, 2004)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IMRT</th>
<th><strong>Late GI toxicity ≥ 2</strong></th>
<th><strong>Late GU toxicity ≥ 2</strong></th>
<th><strong>Impotence</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>75-81 Gy</td>
<td>6% (Kirichenko, 2007) 6% (Jani, 2007) 4% (Zelefsky, 2002) 3% (Shippy, 2007) 2% (Zelefsky, 2006)</td>
<td>23% (Jani, 2007) 19% (Shippy, 2007) 15% (Zelefsky, 2002) 6% (Kirichenko, 2007)</td>
<td>49% (Zelefsky, 2006) 48% (Zelefsky, 2002)</td>
</tr>
</tbody>
</table>
GI toxicity: proctitis

- 14% for 3D-CRT and 4% for IMRT
- Treat 100 patients with IMRT will have 10 fewer cases of proctitis
- NNT = 10 patients
Comparative Clinical Effectiveness

IMRT vs. 3D-CRT for Rx 75-80 Gy

- Good Confidence
  - D: Inferior
  - C: Comparable
  - IMRT: Small
  - A: Mod-Large
  - Net Benefit: Limited Confidence
  - P/U: Low Confidence

- Inferior Net Benefit
- Comparable Net Benefit
- Small Net Benefit
- Mod-Large Net Benefit
Draft Integrated Evidence Rating
Key Findings

- Cost per case of proctitis avoided = $313,000
- Cost per QALY = $706,000
- If risk of proctitis =
  - 25%, cost/QALY = $400,000
  - 75%, cost/QALY = $130,000
- Threshold analysis for cost of IMRT
  - Cost/QALY = $100,000 → $16,900
  - Cost/QALY = $150,000 → $19,100
## Integrated Evidence Rating

**IMRT vs. 3D-CRT Rx 75-80 Gy**

### Comparative Clinical Effectiveness

<table>
<thead>
<tr>
<th>Comparative Effectiveness</th>
<th>Aa</th>
<th>Ab</th>
<th>Ac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior A</td>
<td>Aa</td>
<td>Ab</td>
<td>Ac</td>
</tr>
<tr>
<td>Incremental B</td>
<td>Ba</td>
<td>Bb</td>
<td>IMRT</td>
</tr>
<tr>
<td>Comparable C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Pot/Unprov P/U</td>
<td>Pa</td>
<td>Pb</td>
<td>Pc</td>
</tr>
<tr>
<td>Inadequate I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>

### Comparative Value

- **a** High
- **b** Reasonable/Comparable
- **c** Low
Potential Application of ICER Ratings to Medical Policy
Radiation for low-risk prostate CA

Comparative Clinical Effectiveness

Superior A
- Superior: A
- Incremental: B
- Comparable: C
- Pot/Unprov: P/U
- Inadequate: I

Comparative Value
- High
- Reasonable/Comparable
- Low

- Brachytherapy
- IMRT
- Hypofract Rx
- Proton Beam Therapy
From Tech Assessment to Medical Policy

- **Brachytherapy**
  - No prior auth
  - 0% co-pay
  - Premium price

- **Hypofract Rx**
  - Prior auth
  - 20% co-pay
  - Lower reimbursed price

- **Proton Beam**
  - Prior auth/CED
  - Non-covered
Outstanding elements

- Budget impact
- Ethical considerations
- Research considerations
ERG Feedback

- ICER format: useful?
- What information would you have liked?
  - Draft ratings before the meeting?
- What information did you not find useful?
- Process: a vote, consensus, or some blend for rating determination?
- Best role for patients, clinical experts, and manufacturers?
- Other?
Conclusion and Next Steps

- **IMRT vs. 3D-CRT**
  - Potential for technology assessment with integrated assessment of comparative value to support innovative medical policy

- **Next steps**
  - Pegfilgrastim, virtual colonoscopy
  - Complete appraisals of the “family” of EBRT
  - Establish sustainable funding and strategic models
Thank you!
IMRT Appraisal

Economic Model of Side Effects

Evidence Review Group
June 11, 2007
ICER Appraisal Process: Economic Review

• Key economic questions from scoping committee
• Identify existing economic model
• Contract with developers of existing model or create model to run scenarios that reflect key questions
• Technical review of model: Model Review Group
• Presentation of results to Evidence Review Group
• Final Report
IMRT

• Key Questions from Scoping Committee: reduced side effects
• No existing model that specifically modeled individual side effects
• Commissioned development of simple economic model focusing on side effects
• Technical review
• Evidence review group – clinical and economic evidence
• Recommendations
Overview of Presentation

• Model structure and key assumptions
• Data inputs
  – Transition probabilities
  – Costs
  – Quality adjustments
• Results
• Summary of feedback from Model Review Group
IMRT Economic Model: Key Assumptions (i)

• Cost-effectiveness analysis of IMRT compared with 3D-CRT
• Treatment dose of 75 to 81 Gy for both therapies
• Limited to incidence of treatment-related adverse effects (long-term survival does not differ between treatments)
IMRT Economic Model: Key Assumptions (ii)

• Target population: 69 year old men with clinically localized prostate cancer and low/intermediate recurrence risk
• Payer perspective
  – Did not consider opportunity cost of time, etc.
• Time horizon – lifetime
IMRT Economic Model*

*Model also allows for the occurrence of multiple side effects in a single patient.
IMRT Economic Model: Data inputs

• Data from primary and secondary sources
  – Probabilities: Literature review, expert opinion
  – Utilities: Primary data
  – Costs: Literature review, cost interviews

• Direct medical costs of treating toxicities include costs of:
  – physician visits
  – diagnostic tests
  – procedures
  – prescription medications
# Model Inputs: Probabilities

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>3D-CRT</th>
<th>Time to onset (mo)</th>
<th>Time to resolution (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rectal</strong></td>
<td>0.04(^1)</td>
<td>0.14(^2)</td>
<td>12(^3)</td>
<td>12(^3)</td>
</tr>
<tr>
<td><strong>Urinary</strong></td>
<td>0.15(^1)</td>
<td>0.15(^2,4)</td>
<td>12(^3)</td>
<td>12(^3)</td>
</tr>
<tr>
<td><strong>Sexual</strong></td>
<td>0.50(^4)</td>
<td>0.50(^4)</td>
<td>12(^3)</td>
<td>Lifetime</td>
</tr>
</tbody>
</table>

\(^1\) Zelefsky 2002 (772 patients)  
\(^2\) Zelefsky 2001 (810 patients)  
\(^3\) Zelefsky 1999 (743 patients)  
\(^4\) Clinician-expert guidance secondary to limited data
Clinical Vignette for Patients with GI Toxicity*

• Treatment with 6 month course of anti-inflammatory enemas
• Effective in controlling bleeding in 70% of patients
• Remainder undergo an average of three sigmoidoscopy procedures with ablation, followed by an additional 6 month course of enemas

*Source: clinician interviews and literature review
# Model Inputs: Costs and Quality of Life

<table>
<thead>
<tr>
<th></th>
<th>Cost per case</th>
<th>Utility weight&lt;sup&gt;2,3&lt;/sup&gt; (0 to 1 scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT</td>
<td>$42,450&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>3D-CRT</td>
<td>$10,900&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>Rectal</td>
<td>$2,346</td>
<td>0.612</td>
</tr>
<tr>
<td>Urinary</td>
<td>$954</td>
<td>0.685</td>
</tr>
<tr>
<td>Sexual</td>
<td>$2,113</td>
<td>0.729</td>
</tr>
</tbody>
</table>

<sup>1</sup>Konski 2006, CPT codes  
<sup>2</sup>Personal communication with Dr. Basu, Univ. of Chicago (207 patients, time trade-off method)  
<sup>3</sup>Used to estimate quality-adjusted life-years (QALYs)
Results (i)

• Base case
  – Cost per case averted =
Results (i)

- Base case
  - Cost per case averted = $313,000
Results (i)

• Base case
  – Cost per case averted = $313,000
  – Incremental C/E Ratio =
Results (i)

• Base case
  – Cost per case averted = $313,000
  – Incremental C/E Ratio = $706,000/QALY
Results (i)

- Base case
  - Cost per case averted = $313,000
  - Incremental C/E Ratio = $706,000/QALY

- Sensitivity analysis
  - C/E Ratio = $150K/QALY \rightarrow \text{IMRT cost} =
Results (i)

• Base case
  – Cost per case averted = $313,000
  – Incremental C/E Ratio = $706,000/QALY

• Sensitivity analysis
  – C/E Ratio = $150K/QALY $\rightarrow$ IMRT cost = $19,100
Results (i)

• Base case
  – Cost per case averted = $313,000
  – Incremental C/E Ratio = $706,000/QALY

• Sensitivity analysis
  – C/E Ratio = $150K/QALY $\rightarrow$ IMRT cost = $19,100
  – C/E Ratio = $100K/QALY $\rightarrow$ IMRT cost =
Results (i)

• Base case
  – Cost per case averted = $313,000
  – Incremental C/E Ratio = $706,000/QALY

• Sensitivity analysis
  – C/E Ratio = $150K/QALY → IMRT cost = $19,100
  – C/E Ratio = $100K/QALY → IMRT cost = $16,900
## Results (ii)

<table>
<thead>
<tr>
<th>Risk of Rectal Toxicity (IMRT)</th>
<th>Risk of Rectal Toxicity (3D-CRT)</th>
<th>Cost-effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>7%</td>
<td>25%</td>
<td>$400,000/QALY</td>
</tr>
<tr>
<td>14%</td>
<td>50%</td>
<td>$198,000/QALY</td>
</tr>
<tr>
<td>21%</td>
<td>75%</td>
<td>$130,000/QALY</td>
</tr>
</tbody>
</table>