Proton Therapy for Prostate Cancer: What is it Worth?

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Best Practices for Men’s Health 2012 Update
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Disclosures

NONE
“It Costs More, but Is It Worth More?”

_The New York Times_

January 3, 2012

-Ezekiel Emanuel and Steven Pearson

If you want to know what is wrong with American health care today, exhibit A might be the two new proton beam treatment facilities the Mayo Clinic has begun building… which could cost taxpayers billions of dollars for a treatment that, in many cases, appears to be no better than cheaper alternatives.

There is _no convincing evidence that proton beam therapy is as good as_ — much less better than — cheaper types of radiation for any one of these cancers. There has not been a single randomized trial…

If the United States is ever going to control our health care costs, we have to demand better evidence of effectiveness, and _stop handing out taxpayer dollars with no questions asked._

…it is crazy medicine and unsustainable public policy.

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_The Good, the Bad, and the Ugly_

“In this world, there are two kinds of people, my friend. Those with loaded guns…and those who dig.”

_Blonde (Clint Eastwood)_
The conditions of medical practice are tempting physicians to abandon their commitment to the primacy of patient welfare

The Physician Charter 2002

Lancet 2002
Annals Int Med 2002
The Physician Charter 2002

Three principles:

• Patient welfare
• Patient autonomy
• Social justice

Ten commitments

Lancet 2002
Annals Int Med 2002

The Physician Charter 2002

Commitment to a just distribution of finite resources

• Physicians are required to provide health care that is based on the wise and cost-effective management of limited clinical resources.
• Avoidance of superfluous tests and procedures. The provision of unnecessary services not only exposes one’s patients to avoidable harm and expense but also diminishes the resources available for others.

Lancet 2002
Annals Int Med 2002
Where does prostate cancer fit in?

Prostate Cancer Diagnoses and Death Rates in the U.S. 1975-2007

US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention
Rates are per 100,000 and age-adjusted to the 2000 US Std Population SEER
Who needs screening and who needs treatment?

ProTect UK: trial of the century

Accrued: 2002-8

250,000 men

Randomized by family practice

PSA screening

No screening

2200 Case detection

Surgery

External beam

Active surveillance

700

700

800

Endpoints:
- PCa death
- Metastases
Active surveillance – a prospective study

10 year results from a prospective study:

• Overall survival 85%
• Cause-specific survival 99%
• 2 of 423 patients died of cancer, both treated within one year of diagnosis

Klotz Can J Urol 2005

Why is active surveillance underutilized and what drives treatment for so many?

• Belief that we can save lives
• To reduce the risk of local and distant progression
• To reduce the risk of androgen deprivation
• To lower the PSA
• The word “cancer”
Does Radiation Work?

External radiation improves 10-year survival

Scandinavian randomized trial SPCG-7

*Widmark et al Lancet 2009*

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**Scandinavian randomized trial SPCG-7**  
*Widmark et al Lancet 2009*

- Locally advanced PCa  
  - 77% T3  
  - 23% T1-2 high-grade  
  - N=875

- LHRH agonist

- External radiation

- Androgen antagonist

- Androgen antagonist

- Median FU 7.5 years
Scandinavian randomized trial SPCG-7
Widmark et al Lancet 2009

PSA recurrence

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>Endocrine alone</th>
<th>Endocrine + EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>50</td>
</tr>
</tbody>
</table>

Number at risk

- Androgen: 432, 296, 236, 145, 125, 119
- Combination: 430, 412, 308, 281, 215, 303

Cancer-specific survival

- 12% gain at 10 years

Overall survival

- 10% gain at 10 years

- Clear and significant survival gains
- No QoL disadvantage
NCIC CTG PR.3/ MRC PR07/ SWOG JPR3: Overall Survival

HR=0.77 (95% C.I. 0.61-0.98)  P=0.0331

320 Deaths, 175 ADT alone, 145 RT+ADT

# at Risk

ADT 602 509 213 51
ADT+RT 603 512 232 60

Warde et al Lancet 2011

NCIC CTG PR.3/ MRC PR07/ SWOG JPR3: Disease Specific Survival

HR=0.57 (95% C.I. 0.37-0.78) p=0.001

140 Deaths from Prostate Cancer
89 ADT alone, 51 RT+ADT

# at Risk

ADT 602 509 213 51
ADT+RT 603 512 232 60

Warde et al Lancet 2011
What drives treatment for so many?

- Belief that we can save lives
- To reduce the risk of local and distant progression
- To reduce the risk of androgen deprivation
- To lower the PSA
- The word "cancer"

Our addiction to technology

Gizmo Idolatry

Bruce Leff, MD
Thomas E. Fineapple, MD

JAMA 2008

- Gizmo common sense appeal
- Human love of bells and whistles
- Gizmos as a heroic exploit
- Gizmos minimize risk
- Gizmos as proof of competence
- Gizmos as a revenue source
The Radiation Oncologist's Tool: *The Linear Accelerator*

Radiation therapy for prostate cancer 1992

Conventional external beam
Radiation therapy for prostate cancer 2012

Conventional external beam

Conformal external beam

3-D

IMRT

Proton

High-dose conformal

Ultra-high-dose

SBRT Cyberknife

High dose rate

Low dose rate

Brachytherapy

Brachytherapy/external beam

Any of the above with androgen deprivation

How did it come to this?

Local tumor control problem with radiation therapy in prostate cancer
The solution?

Increase radiation dose

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**High Dose Radiation in Prostate Cancer:**

**Randomized phase III trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>n</th>
<th>ADT</th>
<th>Doses tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC</td>
<td>T1-3</td>
<td>301</td>
<td>-</td>
<td>70 vs 78Gy (3-D)</td>
</tr>
<tr>
<td>PROG</td>
<td>T1-2</td>
<td>393</td>
<td>-</td>
<td>70 vs 79Gy (3-D/P+)</td>
</tr>
<tr>
<td>NKI</td>
<td>T1-3</td>
<td>664</td>
<td>-/+</td>
<td>68 vs 78Gy (3-D)</td>
</tr>
<tr>
<td>MRC</td>
<td>T1-3</td>
<td>843</td>
<td>+</td>
<td>64 vs 74Gy (3-D)</td>
</tr>
<tr>
<td>Hamilton</td>
<td>T1-3</td>
<td>138</td>
<td>-</td>
<td>66 vs 40+30 (HDR)</td>
</tr>
</tbody>
</table>

10-20% benefit in FFBF for 8-10 Gy increase in total dose
PROG 9509: A randomized trial of radiation dose in prostate cancer

Latest analysis (Zietman et al JAMA 2005, JCO 2010)
- Median follow-up 8.9 years

What is the toxicity associated with dose escalation?
### Table 2. Acute and Late GU and GI Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>70.2 GyE In – 1960</th>
<th>73.2 GyE In – 1951</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Acute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GU</td>
<td>72</td>
<td>37</td>
</tr>
<tr>
<td>GI</td>
<td>76</td>
<td>39</td>
</tr>
<tr>
<td>Late</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GU</td>
<td>82</td>
<td>42</td>
</tr>
<tr>
<td>GI</td>
<td>68</td>
<td>35</td>
</tr>
</tbody>
</table>

Abbreviations: GU, genitourinary; GyE, Gray equivalents.
*Testing grade 1 versus others using z test.*
**PROG 9509: A randomized trial of radiation dose in prostate cancer**

Cross-sectional quality of life study on long-term survivors

Validated Prostate Cancer Symptom Index

83% questionnaire response

Median follow-up 9.4 years

Median age 76 years

*Talcott et al JAMA 2010*

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**PROG**

<table>
<thead>
<tr>
<th></th>
<th>70Gy</th>
<th>79Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary obstr/irritn</td>
<td>23.3</td>
<td>24.6</td>
</tr>
<tr>
<td>Bowel</td>
<td>7.7</td>
<td>7.9</td>
</tr>
<tr>
<td>Sexual</td>
<td>68.2</td>
<td>65.9</td>
</tr>
</tbody>
</table>

Symptom scales

0 = no symptoms

100 = maximal distress/dysfunction

*Talcott et al JAMA 2010*
The problem with dose escalation

Higher doses need more accurate delivery:

Hardware and software advances in RT
Better prostate imaging

Improved radiation delivery systems: Hardware and software advances

2-D radiation – 70-90s
Improved radiation delivery systems: Hardware and software advances

3-D Conformal – 90s  Intensity Modulation – 00s

Comparative DVHs: Volume of anterior rectum >70Gy

2-D – 55%  3-D – 30%  IMRT – 18%
MDACC 78 Gy Arm Grade ≥2 late rectal toxicity:
Subdivided by percent rectum treated to ≥70 Gy

![Graph showing rectal reaction over months after radiotherapy]

6 yr Rectal toxicity (2+)
≤25%: 16%
>25%: 46%

Conformal Radiation in Localized Prostate Cancer
Royal Marsden Randomized Trial 1999

Proctitis

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conformal (3D)</td>
<td>37%</td>
</tr>
<tr>
<td>Conventional (2D)</td>
<td>56%</td>
</tr>
</tbody>
</table>

Dearaley et al Lancet 1999
External beam radiation: climbing the technological ladder

- Protons
- IMRT
- 3D-conformal
- Conventional EBRT

Proven advantage

MSKCC: IMRT vs 3DCRT Rectal toxicity

Zelefsky et al J Urol 2001
SEER-Medicare Analysis:
Bowel Complications Requiring an Invasive Procedure

Composite Bowel Complications

Proctitis, Hemorrhage

Bekelman, Efstathiou et al IJROBP 2011

3-D and IMRT comparison

- Clinical benefits for patients
- Windfall for physicians and their hospitals
Utilization of IMRT for Localized Prostate Cancer: SEER analysis

Bekelman, Efstathiou et al IJROBP 2011
The hazards of ultra-conformal therapy:

• Patient motion
• Prostate motion

The solutions:

• Patient immobilization
• Prostate immobilization
• Daily prostate imaging
What is image-guided radiation therapy?

"Image guided therapy"
On-line treatment imaging
Direct vision

Daily ultrasound
“Image guided therapy”
On-line treatment imaging
Direct vision
CONE BEAM

- Insertion under TRUS guidance
- Visible on portal films / portal vision
- 3 for “triangulation”

sagittal, posterior
“Image guided therapy”
On-line treatment imaging
Smart fiducial markers

AC Wireless Magnetic Tracking

Litzenberg et al ASTRO 2005

Use of image-guided radiation therapy

Simpson D et al (UCSD, ASTRO 09)
Cumulative use of in-room image-guided radiation therapy (IGRT) technologies. The total percentage of respondents adopting or discontinuing IGRT utilization is plotted by year.
And now.......proton beam therapy

Aims:

Better tumor eradication through higher doses
Reduced morbidity

Proton beam: the past, the present, and the future

• The physics
• The clinical potential
• The uncertainty
• The business model
Proton beam: the past, the present, and the future

- The physics
- The clinical potential
- The uncertainty
- The business model

Radiation deposition in tissue for photons vs protons

Wilson RR Radiology 1946
Proton Beam...a searchlight without a tail
_is it really this simple?_

Proton beam: the past, the present, and the future

- The physics
- The clinical potential
- The uncertainty
- The business model
Prostate

Excess Radiation Dose:
IMRT vs protons

Courtesy of A. Trofimov
Whole body radiation dose

Excess volume irradiation with IMRT

brachytherapy

If comparing treatment plans……..

LDR

HDR

Brachytherapy always wins!!
Proton Beam Future Possibilities: 
Intensity-modulated proton therapy (IMPT)

Comparative DVHs for IMRT, protons, and IMPT

Trofimov et al IJROBP 2007
Can proton beam be used to deliver high boost doses to part of the prostate?

Proton beam future possibilities: Focal Therapy

Use of diagnostic imaging, image guidance, and sharper beams to focally boost to high dose
Partial Prostate Boost using IMPT

Proton beam: the past, the present, and the future

• The physics
• The clinical potential
• The uncertainty
• The business model
Uncertainty in proton therapy

- Biological
- Physical
- Clinical
- Financial

Uncertainty in proton therapy - physics

- Penumbra
- Inhomogeneity
- Margins
- Neutrons
Penumbra and end-of-range uncertainty

Proton Beam Future Possibilities: Anterior fields

Courtesy of H. Lu, S. Tang
Sensitivity to tissue heterogeneity:
Anatomical variation in femur angle

Fraction 4

Fraction 32

42°

91 mm

26°

79 mm

Sensitivity to tissue heterogeneity

Sensitivity to tissue heterogeneity
Proton beam therapy

Good news: High dose volume is highly conformal

Bad news: Beam not so sharp at prostate depth
Very sensitive to bone density

Uncertainty in proton therapy - clinical

An improved means to an unimproved end?
Is there any proven advantage to these new technologies? Theoretically yes.

Current proton beam

Is proton beam superior to other therapies in terms of prostate cancer control?
Case-matched comparison: Proton beam vs Brachytherapy

Can proton beam be used to escalate radiation dose even further in the treatment of prostate cancer?
ACR 0312: A prospective study of radiation dose escalation to 82Gy in early prostate cancer

Median follow-up 32 months

Late morbidity (GU/GI)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2+</td>
<td>34%</td>
</tr>
<tr>
<td>Grade 3+</td>
<td>8%</td>
</tr>
</tbody>
</table>

Does proton beam carry less morbidity in the treatment of prostate cancer?
Could proton beam reduce morbidity of prostate cancer treatment?

Is there any proven advantage to these new technologies? Clinical trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose</th>
<th>Late GU Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC</td>
<td>78.0 Gy</td>
<td>3D</td>
</tr>
<tr>
<td>RTOG</td>
<td>79.2 Gy</td>
<td>3D</td>
</tr>
<tr>
<td>MSKCC</td>
<td>81.0 Gy</td>
<td>IMRT</td>
</tr>
<tr>
<td>PROG</td>
<td>79.2 Gy</td>
<td>Protons</td>
</tr>
</tbody>
</table>

78-81 Gy safely delivered with 3D photons, IMRT, or protons
Is there any proven advantage to these new technologies? Clinical trials

Two possible explanations:

• Looked for the advantage in the wrong ways
• No clinically significant advantage

Proton beam: the past, the present, and the future

• The physics
• The clinical potential
• The uncertainty
• The business model
Proton beam therapy – US treatment centers

Many more in planning stages – most with a prostate cancer business model
Burr Proton Treatment Center - MGH

Price tag in 2012: $150-200 million

Repaying the debt on a proton beam center

Dependent on reimbursement
Dependent upon installation costs
Dependent upon patient mix
Depends upon the terms of the loan

7 – 30 year repayment plans
Repaying the debt on a proton beam center

Pressure to reduce costs:

• Simplification of therapy
• Leave out upgrades
• Stuck with prototype machines
• Avoid treating those most in need

Repaying the debt on a proton beam center

<table>
<thead>
<tr>
<th>Prostate</th>
<th>Pediatric Medullo</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mins</td>
<td>60-90 mins</td>
</tr>
</tbody>
</table>
Classical market behavior
Supply and demand

European/Canadian medical market behavior
Technology/therapy evaluation
Regulated supply

US medical market behavior
Supply-led demand
Code-driven supply
Advocacy-led demand
Cost-Effectiveness

“Proton beam therapy is not cost effective for most patients with prostate cancer using the commonly accepted standard of $50,000/QALY.”

Cost-Effectiveness

“Proton beam therapy is both less effective and more costly than either brachytherapy or IMRT.”
Future of New Technology

The adoption and dissemination of "unproven" emerging technology into healthcare delivery has the risk of:

- Distorting patterns of health care
- Paradoxically leading to over-treatment of patients
- Sucking resources from areas of medical need
- Driving hospitals to the edge of financial ruin
- Drawing attention to and discrediting uro-oncology

New technology and the enthusiasm curve
One Solution: Regulation

- Continued reimbursement for prostate cancer
- End reimbursement
- Payment for limited indications
- Co-pay
- "Certificates of need"
- Coverage with evidence development

Another Solution:

Evidence Development
"The Magic Bullet Falls Short"

Study questions proton therapy for prostate cancer

Sheets et al. JAMA 2012

Changes in Patient Reported Bowel Function: Protons vs IMRT

Gray, Efstathiou, Prost-QA consortium (GU ASCO 2012)
Filling the Evidence Gap:  
Level 1 Evidence

Randomized Controlled Trial:  
MGH, UPenn  
Wash U, ITC  
NCI, RTOG  
Vendors, Insurers  
Patients, Clinicians  
Policy makers

Low-intermediate risk  
Prostate cancer

IMRT  
79 Gy

Protons  
79 CGE

Patient-Reported Quality of Life Endpoints

May 14, 2012
For years, doctors and federal health agencies have called for a scientific study like the one led by Mass. General, which will enroll its first patients by early June.

…the medical community are eager for hard evidence, and the question is becoming increasingly important as controlling health care costs becomes an increasingly higher priority.

“Is the additional cost for proton beam therapy worth it?”
Filling the Evidence Gap: *Alternative Methodologies*

**National Radiation Oncology Registry:**
- Observational study infrastructure
- Electronic linkage of institutions
- Prostate cancer as the pilot
- Longitudinal data on efficacy and morbidities
- Patient-reported quality of life endpoints
- Incorporate innovation and monitor change in practice
- Evaluate process associated with improved outcomes

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**The Future of New Technology:**

*Decreased Cost*

Can these new technologies be used to lower the cost of care or to increase patient convenience?
Hypofractionation
(i.e. fewer, larger fractions)

- Patient convenience
- Better resource utilization
- Lower treatment costs
- Potential for therapeutic gain

Hypofractionation: *Is 8 weeks really necessary?*

Randomized trials:

- MRC UK: 7.5 vs 4 weeks
- NCIC: 8 vs 5 weeks
- RTOG: 8 vs 5.5 weeks
Will these new technologies allow extreme hypofractionation in the treatment of prostate cancer?

*How low can you go?*

**RTOG 0938: Phase II Randomized Hypofractionation Trial**

*Low Risk Prostate Cancer*

- 174 patients (Protons, IMRT, Cyberknife)
- 36.25 Gy/7.25Gy x5
- 51.6 Gy/4.3 Gy x12

Endpoints
- QOL, Toxicity
The future of proton therapy

We need proton therapy

Ideally:
• geographically well-distributed
• consortia based around academic centers
• heavy emphasis on peds
• heavy emphasis on research
Proton beam is an excellent treatment for prostate cancer...

...as are radical prostatectomy, 3DCRT, IMRT, brachytherapy, and active surveillance.

New is not always better!

*The law of diminishing returns*

- Cost
- Time
- Prostate dose limit
Closing Thoughts

• External beam radiation therapy is a safe and effective treatment and dose escalation improves cancer control

• Technology is great but it is seductive and it is expensive

• Technology can be used creatively to
  spare normal tissue
  increase dose and dose per fraction
  account for motion
  localize and boost tumor
  reduce overall treatment time

Closing Thoughts

• Technology can be used equally creatively to
  increase billing
  income boosting

• If all forms of high dose radiation are comparably efficacious then need QoL and economic analyses to determine their true justification and appropriate use

• American medicine can no longer afford expensive therapies of uncertain benefit; yet, we must continue to invest in and promote scientific innovation and creativity