



## Is brachytherapy the Most *Valuable* Player (MVP) for prostate cancer?

Mitchell Kamrava, MD  
Assistant Clinical Professor  
Department of Radiation Oncology  
University of California Los Angeles

### Disclosures

- Speaking honorarium from Elekta in 2014



## Outline

- Comparative effectiveness research (CER)
- The localized prostate cancer problem
- Prostate CER literature
- The brachytherapy problem

REPORT BRIEF • JUNE 2009

### INITIAL NATIONAL PRIORITIES FOR COMPARATIVE EFFECTIVENESS RESEARCH



*CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.*

IOM. National Academies Press. 2009.



## Why is CER needed?

- Limitations of RCT
  - Costs
  - Accrual issues
    - SPIRIT Trial (Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial)
  - Duration to complete
    - SWOG 8794 trial of adjuvant RT
  - Results may not be generalizable

REPORT BRIEF • JUNE 2009

### INITIAL NATIONAL PRIORITIES FOR COMPARATIVE EFFECTIVENESS RESEARCH



**LIST OF PRIORITY TOPICS BY QUARTILE RATINGS  
(DISPLAY WITHIN QUARTILE DOES NOT INDICATE PRIORITY RANK).**

Compare the effectiveness of management strategies for localized prostate cancer (e.g., active surveillance, radical prostatectomy [conventional, robotic, and laparoscopic], radiotherapy [conformal, brachytherapy, proton-beam, and intensity-modulated radiotherapy]) on survival, recurrence, side effects, quality of life, and costs.

10 options to consider if you include HDR and SBRT

IOM. National Academies Press. 2009.



## pcori | Patient-Centered Outcomes Research Institute

- Established in 2010 through Patient Protection and Affordable Care Act (PPACA) as an independent non-profit organization
- Budget:
  - \$160 million in 2012
  - > \$500 million per year by 2014
- Funding source:
  - annual transfers from Medicare trust fund
  - per-capita fee assessed from private health insurers
- Caveats:
  - Can't include mandates for coverage or payment
  - Can't use dollar QALY or similar cost effectiveness threshold as part of recommendations

Pearson S. JCO. 2012.

## The localized prostate cancer problem

- NIH estimates overall direct cost of cancer care in US in 2010 was:
  - \$102.8 billion**
- Prostate cancer (5<sup>th</sup> most costly cancer)
  - **\$12 billion** annual costs in 2010
  - **\$19 billion** projected in 2020

Nguyen P et al. JCO. 2011.



## Treatment selection dilemma

Printed by mitchell.karrara on 5/18/2014 6:02:13 PM. For personal use only. Not approved for distribution. Copyright © 2014 National Comprehensive Cancer Network, Inc., All Rights Reserved.

**NCCN National Comprehensive Cancer Network®** **NCCN Guidelines Version 2.2014 Prostate Cancer** [NCCN Guidelines Index](#) [Prostate Table of Contents](#) [Discussion](#)

RISK GROUP	EXPECTED PATIENT SURVIVAL <sup>a</sup>	INITIAL THERAPY	ADJUVANT THERAPY
Low: • T1-T2a • Gleason score ≤6 • PSA <10 ng/mL	≥10 y <sup>b</sup>	<p><b>Active surveillance<sup>f</sup></b>                      • PSA no more often than every 6 mo unless clinically indicated                      • DRE no more often than every 12 mo unless clinically indicated                      • Repeat prostate biopsy no more often than every 12 mo unless clinically indicated</p> <p><b>RT<sup>g</sup> or brachytherapy</b></p> <p><b>RP<sup>h</sup> ± PLND if predicted probability of lymph node metastasis ≤2%</b></p>	<p>Adverse features:<sup>i</sup>                      RT<sup>g</sup> or Observation<sup>j</sup></p> <p>Lymph node metastasis:                      ADT<sup>k</sup> (category 1) ± RT<sup>g</sup> (category 2B) or Observation<sup>j</sup></p> <p>See <a href="#">Monitoring (PROS-6)</a></p>
	<10 y <sup>b</sup>	Observation <sup>l</sup>	

<sup>a</sup>See Principles of Life Expectancy Estimation (PROS-A).  
<sup>b</sup>The Panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing. See [NCCN Guidelines for Prostate Cancer Early Detection](#). Active surveillance is recommended for these subsets of patients.  
<sup>c</sup>Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. See Principles of Active Surveillance and Observation (PROS-C).  
<sup>d</sup>See Principles of Radiation Therapy (PROS-D).  
<sup>e</sup>See Principles of Surgery (PROS-E).  
<sup>f</sup>Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.  
<sup>g</sup>Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).  
<sup>h</sup>See Principles of Androgen Deprivation Therapy (PROS-F).  
<sup>i</sup>Note: All recommendations are category 2A unless otherwise indicated.  
<sup>j</sup>Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 2.2014, 04/01/14 © National Comprehensive Cancer Network, Inc., 2014. All rights reserved. This document and this illustration may not be reproduced in any form without the express written permission of NCCN. **PROS-3**

### LOW-RISK PROSTATE CANCER MANAGEMENT DECISION GUIDE

	Active Surveillance	Radical Prostatectomy	Brachytherapy	IMRT
Potential Comparative Advantages	~40% never show clinical progression requiring active treatment	Single procedure Low risk of bowel side effects	Single procedure Minimally invasive Lower risks of short-term incontinence or impotence than surgery	Non-invasive Lower risks of short-term incontinence or impotence than surgery
Potential Comparative Disadvantages	Risk of "missed" aggressive tumors or tumor progression Monitoring and biopsies required	Surgical complications Higher rates of short-term incontinence and impotence	Risk of short-term urinary obstruction	Higher (~45) number of visits for treatment Higher risk of bowel side effects (proctitis)
May Not Be Best For	Extended life expectancy (>20 yrs) High anxiety High potential for failure to follow-up	Higher surgical risks Higher concern for sexual function and urinary continence	Large prostate History of urinary obstruction	Higher concern for normal bowel function
Relative Cost to Insurers	↓	↔	↔	↑

Institute for clinical and economic review (ICER)



## Active Surveillance Compared With Initial Treatment for Men With Low-Risk Prostate Cancer A Decision Analysis

- 65 yo male with low risk prostate cancer
- Comparison of:
  - Brachytherapy (LDR)
  - IMRT
  - Radical prostatectomy
  - Active surveillance
- Main outcome measure:
  - Quality-adjusted life year (QALY)

Hayes J et al. JAMA. 2010.

## Calculating QALY

**Table 2.** Model Inputs for Utilities for Health States<sup>a</sup>

Health State	Utility (SD) [Range]
Prostate cancer	
Active surveillance <sup>26</sup>	0.83 (0.24) [0.42-1]
Biochemical recurrence	0.68 (0.26) [0.34-1]
Metastatic cancer	0.12 (0.18) [0.06-0.24]
Treatment of adverse effects	
Impotence	0.88 (0.20) [0.44-1]
Urinary difficulty	0.88 (0.16) [0.44-1]
Urinary incontinence	0.81 (0.30) [0.40-1]
Bowel problems	0.63 (0.32) [0.32-1]
Impotence and urinary difficulty	0.77 (0.24) [0.38-1]
Impotence and urinary incontinence	0.84 (0.23) [0.42-1]
Urinary incontinence and bowel problems	0.64 (0.33) [0.32-1]
Impotence and bowel problems	0.55 (0.35) [0.23-1]
Impotence, urinary incontinence, and bowel problems	0.38 (0.30) [0.19-0.75]
Major complications of radical prostatectomy <sup>b</sup>	0.96 (0.012) [0.48-1]
Minor complications of radical prostatectomy <sup>c</sup>	1
Other health states	
Posttreatment without adverse effects <sup>26</sup>	0.80 (0.24) [0.4-1]
Treatment with radical prostatectomy <sup>d</sup>	0.46 (0.36) [0.23-0.92]
Treatment with radiation therapy <sup>d</sup>	1 [0.5-1]

<sup>a</sup>Utilities are from Stewart et al<sup>27</sup> and unpublished data (Stewart et al; 2009) except as otherwise noted.  
<sup>b</sup>Weighted average of disutilities of component complications (major bleeding, deep vein thrombosis/pulmonary embolism, systemic infection, myocardial infarction/cerebrovascular accident, bowel injury) from Sullivan and Ghushchyan.<sup>28</sup>  
<sup>c</sup>Because minor surgical complications did not involve significant treatment, no decrement in utility was assigned to these complications.  
<sup>d</sup>The treatment with radical prostatectomy utility reflected only the utility for undergoing radical prostatectomy without complications, erectile dysfunction, or urinary symptoms. No utility was found in the literature that reflected only the utility for undergoing radiation therapy without adverse effects; sensitivity analysis was performed on a wide range.

Hayes J et al. JAMA. 2010.



## AS provided 6 m of additional QALY compared with brachy

**Table 3.** Probabilistic Sensitivity Analysis

Strategy	QALYs (95% Confidence Interval)	Incremental QALY
Active surveillance	11.00 (6.93-13.90)	
Brachytherapy	10.65 (5.57-14.29)	-0.35
IMRT	10.54 (5.55-14.27)	-0.09
Radical prostatectomy	10.30 (4.89-14.36)	-0.24

Abbreviations: IMRT, intensity-modulated radiation therapy; QALY, quality-adjusted life-year.

Hayes J et al. JAMA. 2010.

## Primary treatments for clinically localised prostate cancer: a comprehensive lifetime cost-utility analysis

Matthew R. Cooperberg, Naren R. Ramakrishna<sup>1</sup>, Steven B. Duff<sup>\*</sup>, Kathleen E. Hughes<sup>2</sup>, Sara Sadownik<sup>1</sup>, Joseph A. Smith<sup>5</sup> and Ashutosh K. Tewari<sup>6</sup>

**Table 5** Mean discounted costs, QALYs and undiscounted survival.

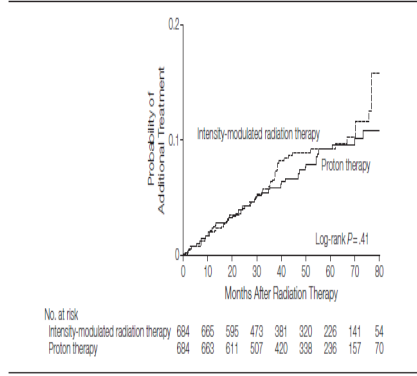
Treatment method	Mean (sd)			
	Costs, \$	QALYs	Life years	% prostate cancer death
Low risk				
EBRT+BT	40 588 (3573)	10.7 <sup>§</sup> (0.5)	16.2 (0.7)	7.4 (3.9)
BT	25 067 <sup>†</sup> (2213)	10.8 <sup>§</sup> (0.5)	16.2 (0.7)	6.9 (2.8)
3DCRT	27 626 (1830)	10.3 (0.4)	15.5 (0.6)	12.1 (2.4)
IMRT	37 718 (3033)	10.8 <sup>§</sup> (0.4)	16.2 (0.7)	6.9 (2.7)
ORP	20 245 <sup>*</sup> (2701)	11.3 <sup>†</sup> (0.4)	16.7 (0.6)	2.6 (2.1)
RARP	19 901 <sup>*</sup> (2684)	11.3 <sup>†</sup> (0.4)	16.7 (0.6)	2.7 (1.9)
LRP	20 497 <sup>*</sup> (2877)	11.3 <sup>†</sup> (0.4)	16.7 (0.6)	2.7 (2.1)

No differences were found between surgical methods for cost or QALYs. <sup>\*</sup>Significantly less expensive than each RT method (P < 0.001). <sup>†</sup>Significantly more effective than each RT method (P = 0.008). <sup>‡</sup>Significantly less expensive than other RT methods (P < 0.001). <sup>§</sup>Significantly more effective than 3DCRT (P < 0.001). <sup>¶</sup>Significantly more effective than other RT methods (P < 0.001). <sup>\*\*</sup>Significantly less expensive than EBRT+BT and IMRT (P < 0.001).



## Intensity-Modulated Radiation Therapy, Proton Therapy, or Conformal Radiation Therapy and Morbidity and Disease Control in Localized Prostate Cancer

**Figure 2.** Propensity Score-Matched Rates of Additional Cancer Treatment for Patients Treated With Intensity-Modulated Radiation Therapy vs Proton Therapy



Outcome per 100 Person-Years	Propensity Score Matched <sup>a</sup>						IMRT vs PT, Rate Ratio (95% CI)
	IMRT (n = 684)			Proton (n = 684)			
	Total Events	100 Person-Years	Rate	Total Events	100 Person-Years	Rate	
Gastrointestinal events	302	17	17.7	347	16.2	21.4	0.82 (0.70-0.97)
Procedures (including colonoscopy)							
Diagnoses	235	19	12.2	301	16.9	17.8	0.66 (0.55-0.79)
Urinary nonincontinence events							
Procedures <sup>b</sup>	44	25	1.8	42	25.8	1.6	1.06 (0.69-1.63)
Diagnoses	161	22	7.5	144	22.9	6.3	1.25 (0.99-1.58)
Urinary incontinence events							
Procedures	161	21	7.6	173	22.1	7.8	0.97 (0.77-1.20)
Diagnoses <sup>c</sup>	75	24	3.1	82	24.8	3.3	0.96 (0.70-1.32)
Erectile dysfunction events							
Procedures <sup>c</sup>	21	25	0.8	36	26.2	1.4	0.61 (0.35-1.06)
Diagnoses	145	22	6.6	164	22.2	7.4	0.89 (0.70-1.12)
Hip fracture <sup>d</sup>	21	26	0.8	18	26.6	0.7	
Additional cancer therapy	58	26	2.2	52	27.5	1.9	1.26 (0.86-1.84)

JAMA, April 18, 2012—Vol 307, No. 15

## Cost of Protons



“I’m stunned,” said Dr. John Santa, a director of Consumer Reports Health. “Did they use a proton beam for this?”





### Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer

Anju Parthan<sup>1\*</sup>, Narin Pruttivarsin<sup>1</sup>, Diane Davies<sup>2</sup>, Douglas C. A. Taylor<sup>1</sup>, Vivek Pawar<sup>3</sup>, Akash Bijlani<sup>2</sup>, Kristen Hassmiller Lich<sup>4</sup> and Ronald C. Chen<sup>4</sup>

- 65 yo male with localized prostate cancer
- Used Markov model to estimate costs over lifetime horizon
- Long term disease control assumed to be equal

Table 6 | Cost-effectiveness results for all comparator treatments for the base-case.

	Total per patient		Incremental		ICER Costs/ QALY gained
	Costs	QALYs	Costs	QALYs	
<b>PAYER PERSPECTIVE</b>					
SBRT	\$24,873	8.11	–	–	Reference
IMRT	\$33,068	8.05	\$8,195	–0.062	Dominated*
PT	\$69,412	8.06	\$44,539	–0.047	Dominated
<b>SOCIETAL PERSPECTIVE<sup>†</sup></b>					
SBRT	\$25,097	8.11	–	–	Reference
IMRT	\$35,088	8.05	\$9,991	–0.062	Dominated
PT	\$71,657	8.06	\$46,560	–0.047	Dominated

ICER, incremental cost-effectiveness ratio; IMRT, intensity-modulated radiation therapy; QALY, quality-adjusted life year.

NOTE: Results are estimated for a patient 65 years old using Medicare reimbursement rates.

\*Dominated – higher cost and lower QALY.

<sup>†</sup>Societal perspective also includes productivity costs owing to time spent in treatment.

### Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer: Comparison of Toxicity

James B. Yu, Laura D. Cramer, Jeph Herrin, Pamela R. Soulos, Arnold L. Potosky, and Cary P. Gross

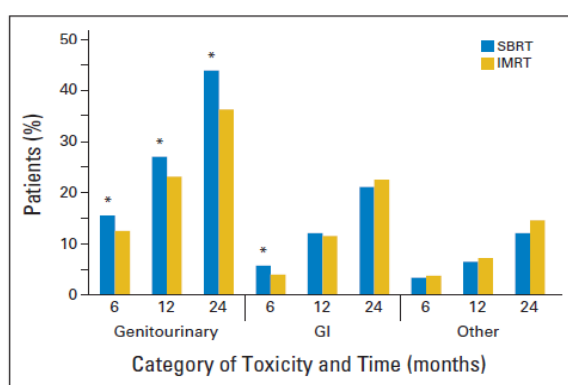


Fig 1. Rate of treatment-related toxicity by time period for patients receiving stereotactic body radiation therapy (SBRT) versus intensity-modulated radiation therapy (IMRT). (\*) Statistically significant difference between SBRT and IMRT.



## Doctors as “death panels”?

BUSINESS DAY

The New York Times

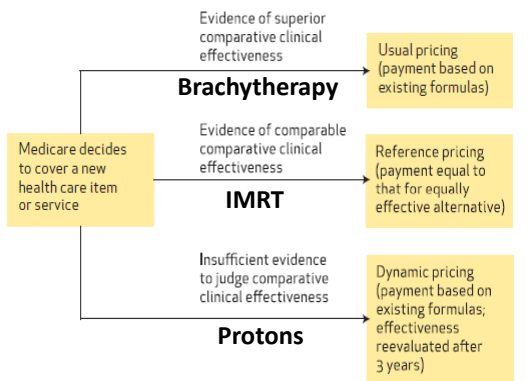
### *Cost of Treatment May Influence Doctors*

By ANDREW POLLACK APRIL 17, 2014

Saying they can no longer ignore the rising prices of health care, some of the most influential medical groups in the nation are recommending that doctors weigh the costs, not just the effectiveness of treatments, as they make decisions about patient care.

## How Medicare Could Use Comparative Effectiveness Research In Deciding On New Coverage And Reimbursement

Using Comparative Effectiveness Research To Determine Medicare Coverage And Reimbursement



COVERED

CO-PAY

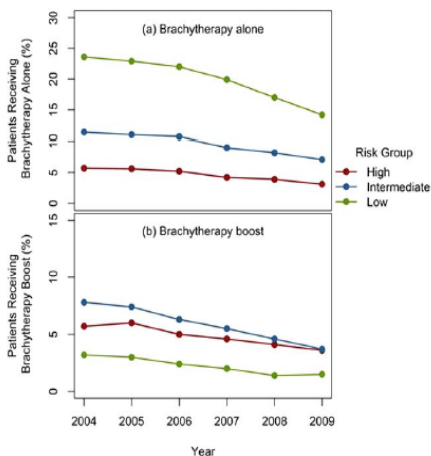
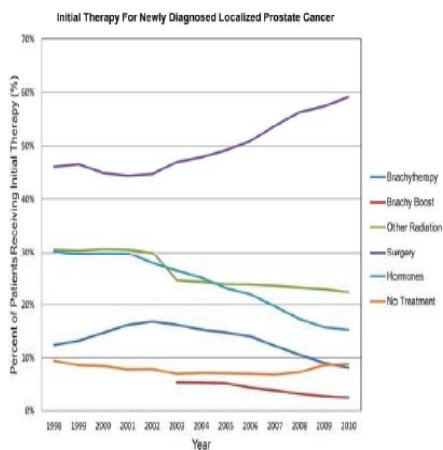
NON-COVERED  
or REFERENCE  
PRICING

Pearson S. Health Affairs. 2010.



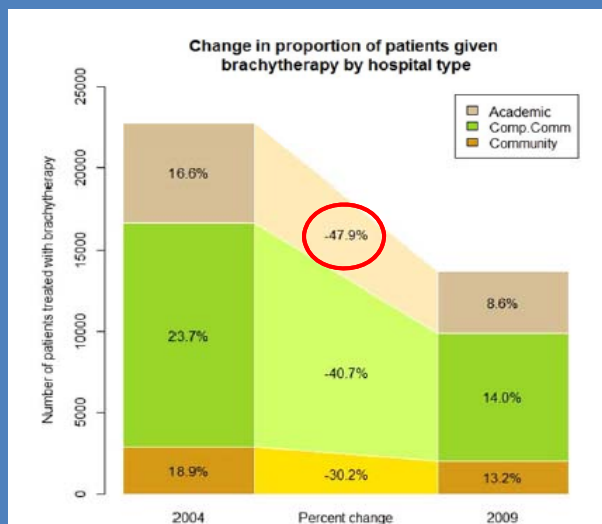
### The Rise and Fall of Prostate Brachytherapy: Use of Brachytherapy for the Treatment of Localized Prostate Cancer in the National Cancer Data Base

Jeffrey M. Martin, MD, MS<sup>1</sup>; Elizabeth A. Handorf, PhD<sup>2</sup>; Alexander Kutikov, MD<sup>3</sup>; Robert G. Uzzo, MD<sup>3</sup>; Justin E. Bekelman, MD<sup>4</sup>; Eric M. Horwitz, MD<sup>1</sup>; and Marc C. Smaildone, MD, MSHP<sup>5</sup>



Cancer Month 00, 2014

## Where is the decline occurring?



**Figure 3.** Receipt of prostate brachytherapy is shown by type of facility. Comp. Comm. indicates comprehensive community cancer program.

Cancer Month 00, 2014



## Conclusions

- Brachytherapy is the MVP
  - Cost effective
  - Excellent long term oncologic outcomes
  - Relatively low acute/late morbidity
- Payment structure in the United States must be reevaluated to improve utilization of brachytherapy over EBRT