Collaborative Models for Technology Assessment and Utilization:
Protons vs IMRT for Prostate Cancer

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Appropriate Use of Advanced Technologies for

Radiation Therapy and Surgery in Oncology Workshop

National Cancer Policy Forum, The National Academies, Institute of Medicine

July 21, 2015

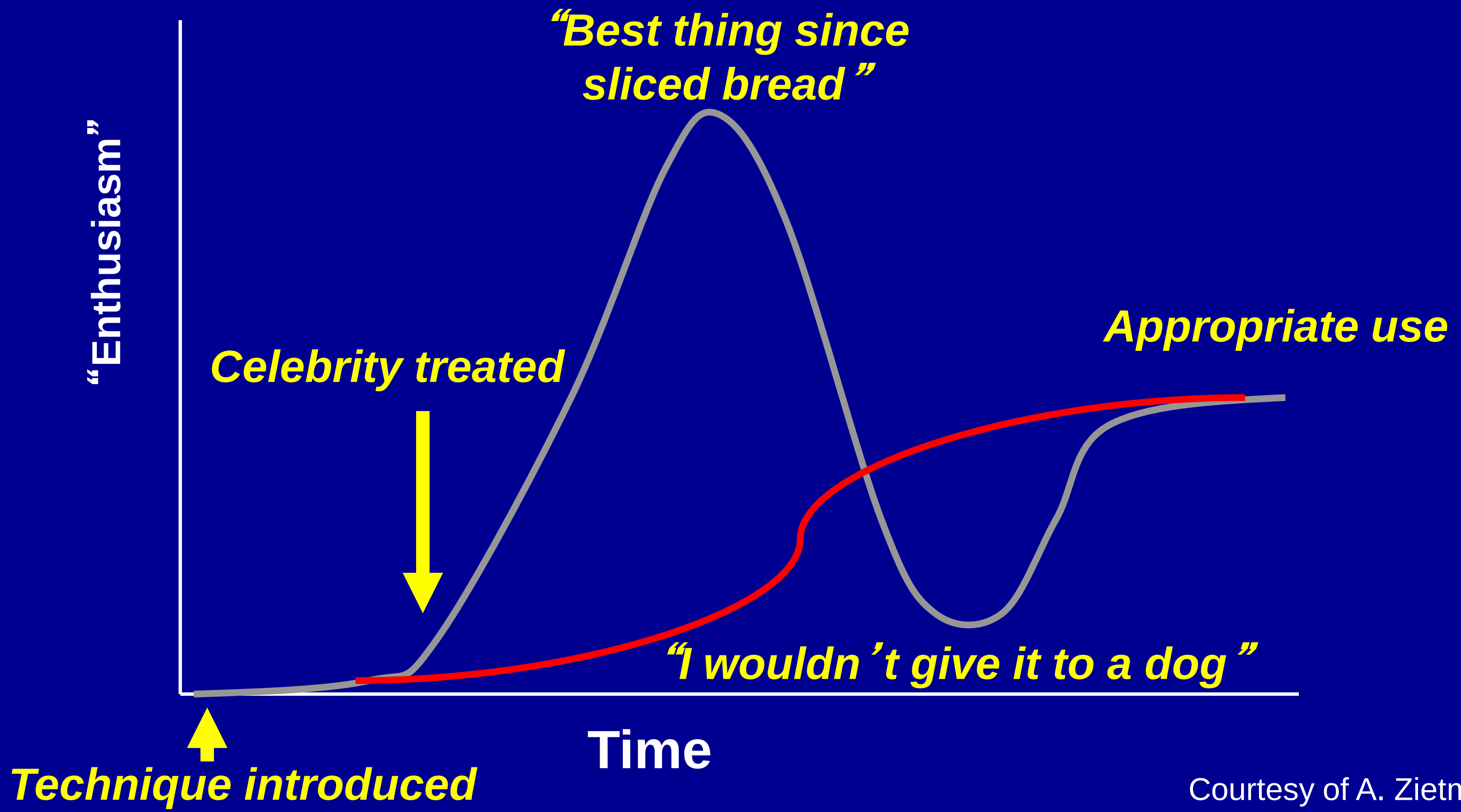
Gizmo Idolatry

Bruce Leff, MD

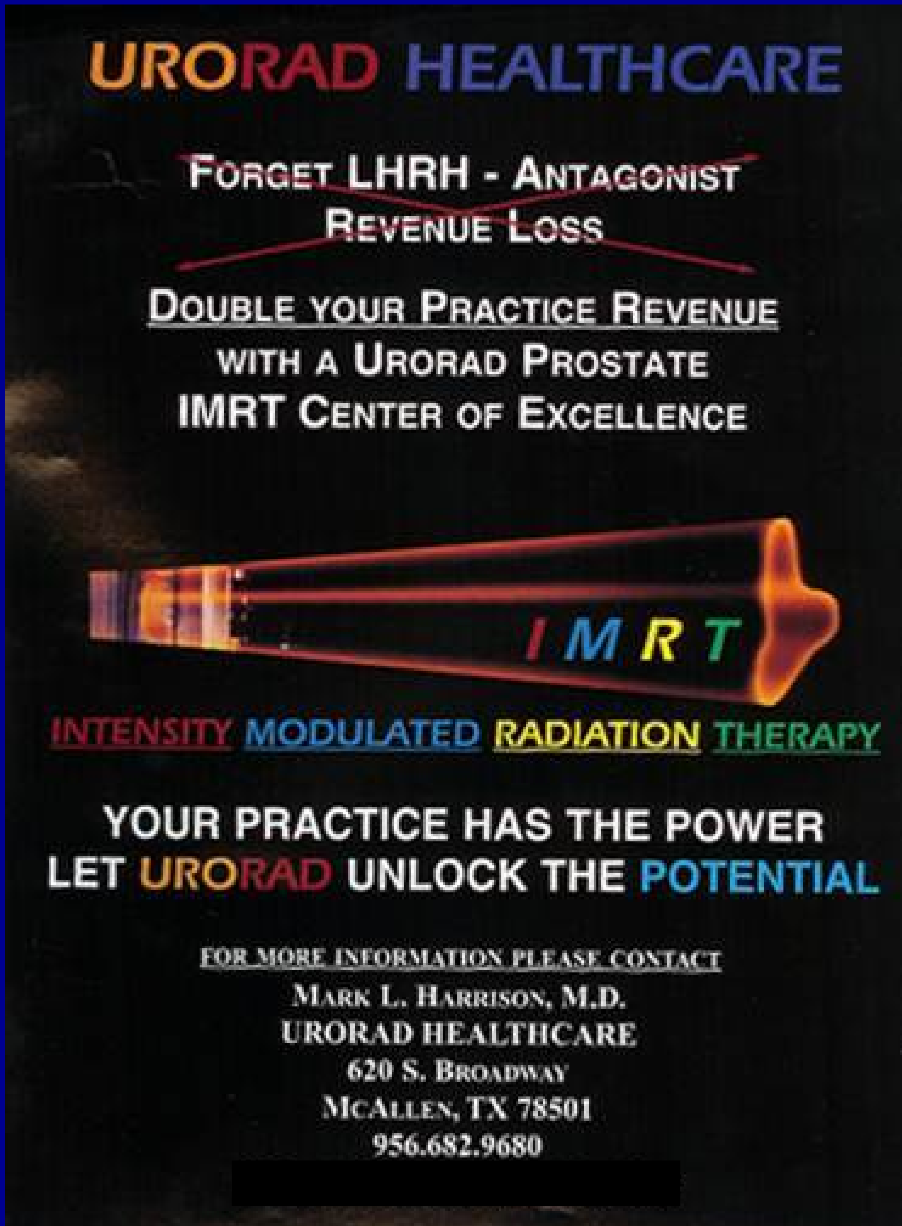
Thomas E. Finucane, MD

Leff B & Finucane TE *JAMA 2008; 299: 1830-1832.*

New technology and the enthusiasm curve



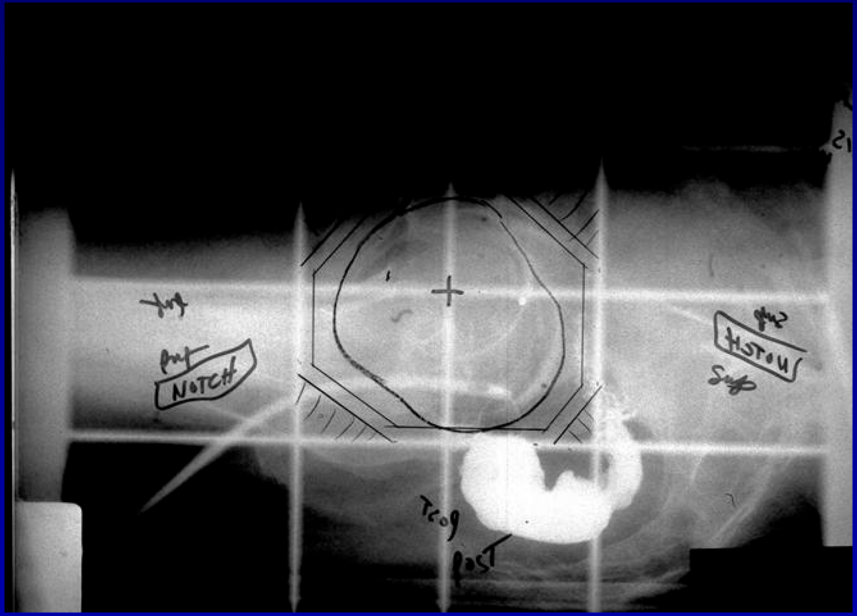
Courtesy of A. Zietman



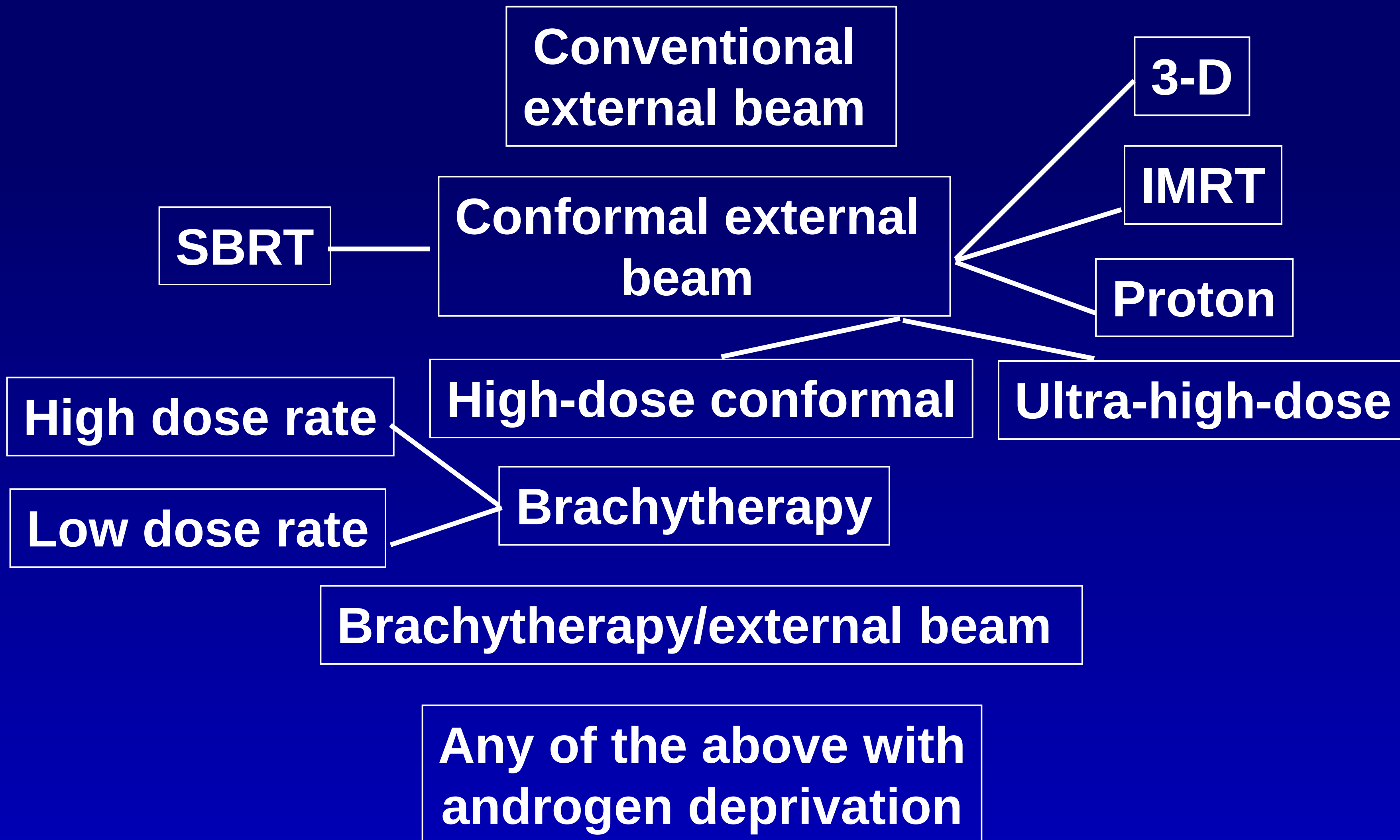
"The sharpness of a surgeon's knife
The softness of an artist's brush"

Radiation therapy for prostate cancer 1995

Conventional external beam



Radiation therapy for prostate cancer 2015



How did it come to this?

Local tumor control problem with radiation therapy in prostate cancer

The solution?

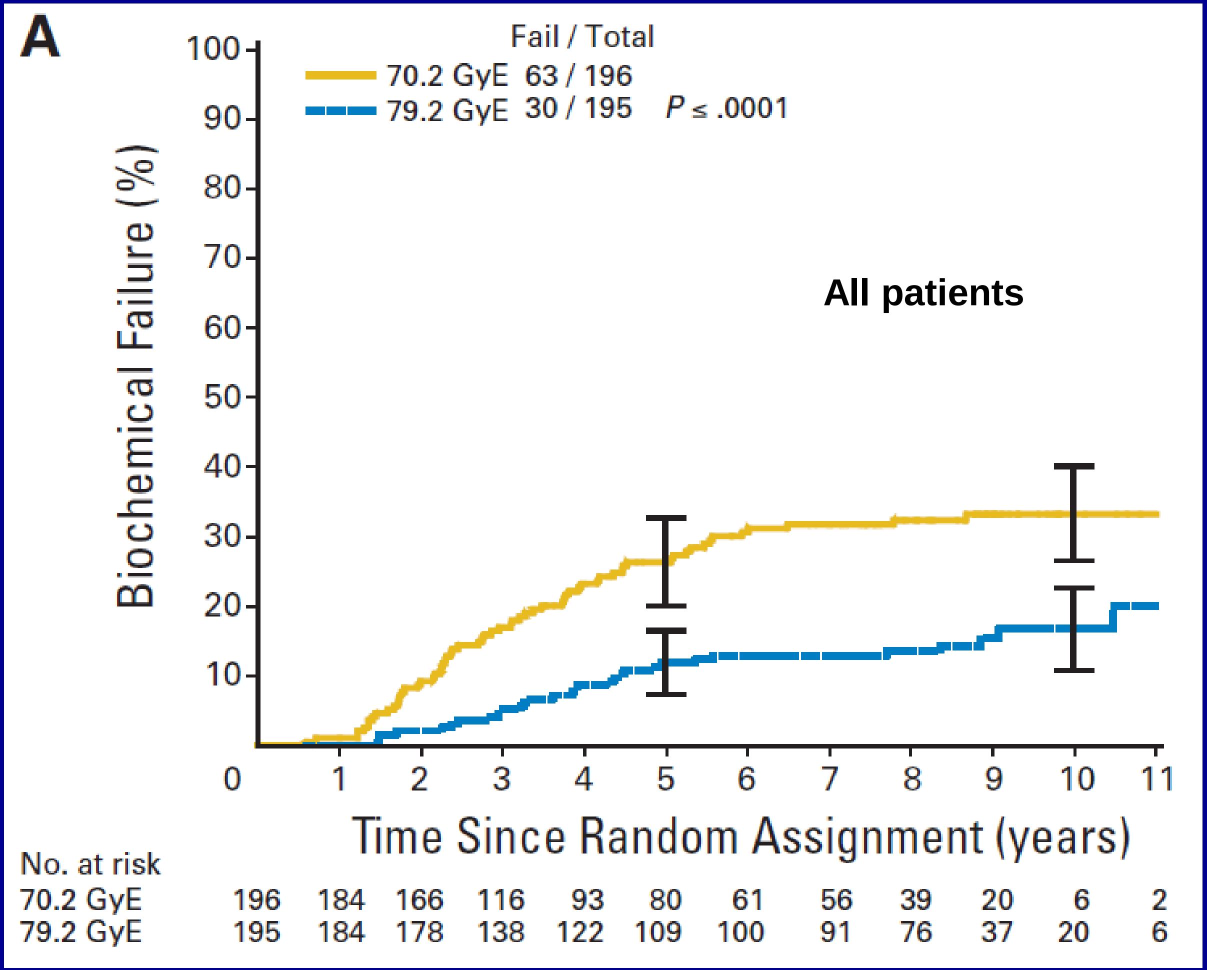
Increase radiation dose

High Dose Radiation in Prostate Cancer: Randomized phase III trials

Trial		stage	n	ADT	Doses tested
MDACC	2008	T1-3	301	-	70 vs 78Gy (3-D)
PROG	2010	T1-2	393	-	70 vs 79Gy (3-D/P+)
NKI	2008	T1-3	664	-/+	68 vs 78Gy (3-D)
MRC	2007	T1-3	843	+	64 vs 74Gy (3-D)
Hamilton	2005	T1-3	138	-	66 vs 40+30 (HDR)

10-20% benefit in FFBF for 8-10 Gy increase in total dose

PROG 9509: A Randomized Trial of Radiation Dose in Prostate Cancer[1,2]



- **Latest analysis: Median follow-up 8.9 years**

1. Zietman AL, et al. *JAMA* 2005; 294:1233-1239.
2. Zietman AL, et al. *J Clin Oncol* 2010; 28:1106-1111.

PROG

Table 2. Acute and Late GU and GI Toxicity

	Assigned Dose																
	70.2 GyE (n = 196)								79.2 GyE (n = 195)								
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1		Grade 2		Grade 3		Grade 4		
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	*P*
Acute																	
GU	72	37	100	51	5	3	0	0	56	29	117	60	4	2	1	1	.0745
GI	76	39	87*	44	2	1	0	0	50	26	123*	63	2	1	0	0	.0006*
Late																	
GU	82	42	44	22	4	2	0	0	88	45	52	27	3	2	0	0	.7934
GI	68	35	25	13	0	0	0	0	79	41	46	24	2	1	0	0	.0895

Abbreviations: GU, genitourinary; GyE, Gray equivalents.
*Testing grade 1 versus others using χ^2 test.

1. Zietman AL, et al. *JAMA* 2005; 294:1233-1239.
2. Zietman AL, et al. *J Clin Oncol* 2010; 28:1106-1111.

PROG

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2. Zietman AL, et al. *J Clin Oncol* 2010; 28:1106-1111.

PROG

	70Gy	79Gy
Urinary obstr/irritn	23.3	24.6
Bowel	7.7	7.9
Sexual	68.2	65.9

Symptom scales

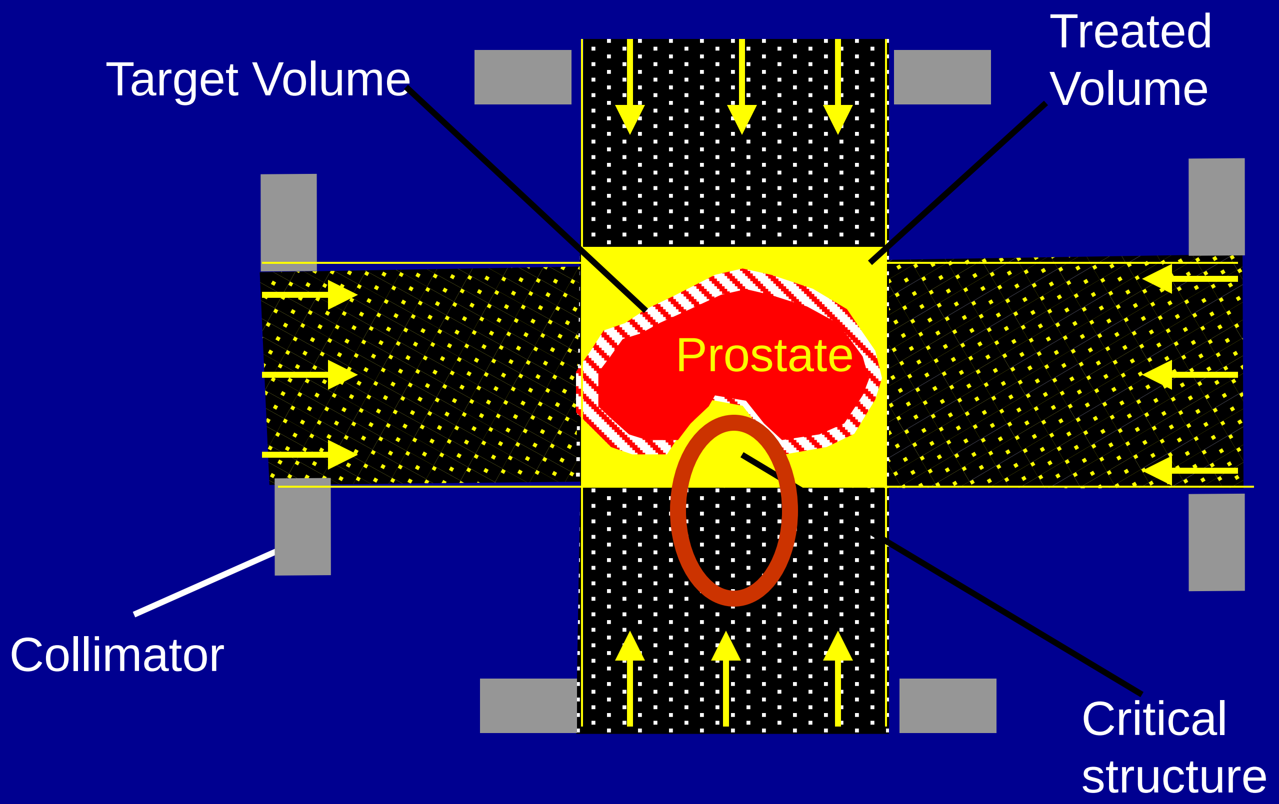
0 = no symptoms

100 = maximal distress/dysfunction

Talcott JA, et al. *JAMA* 2010; 303: 1046-1053.

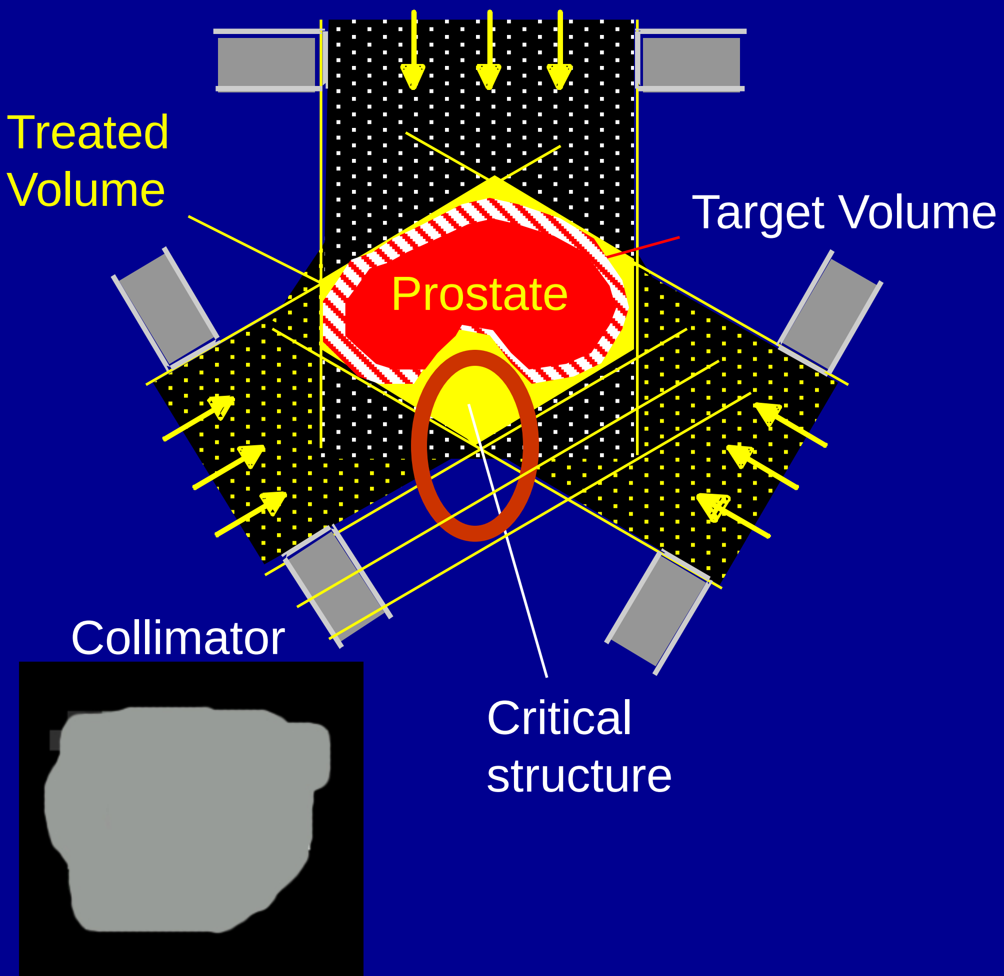
Improved radiation delivery systems: Hardware and software advances

2-D radiation – 70-90s

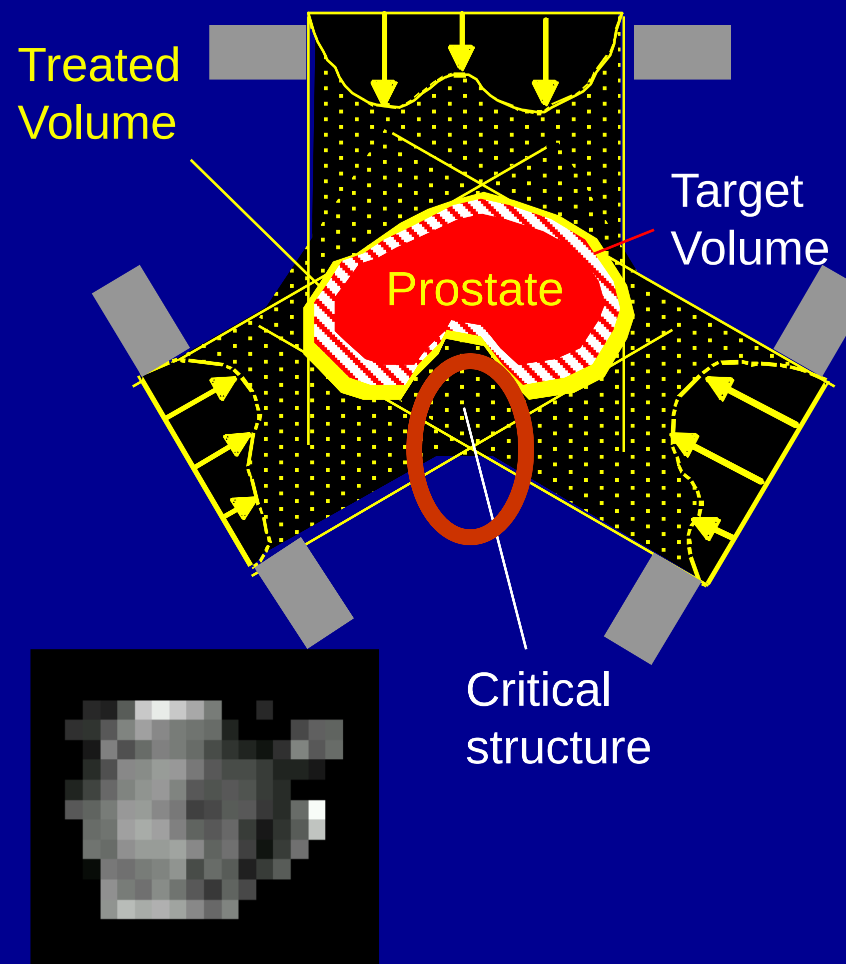


Improved radiation delivery systems: Hardware and software advances

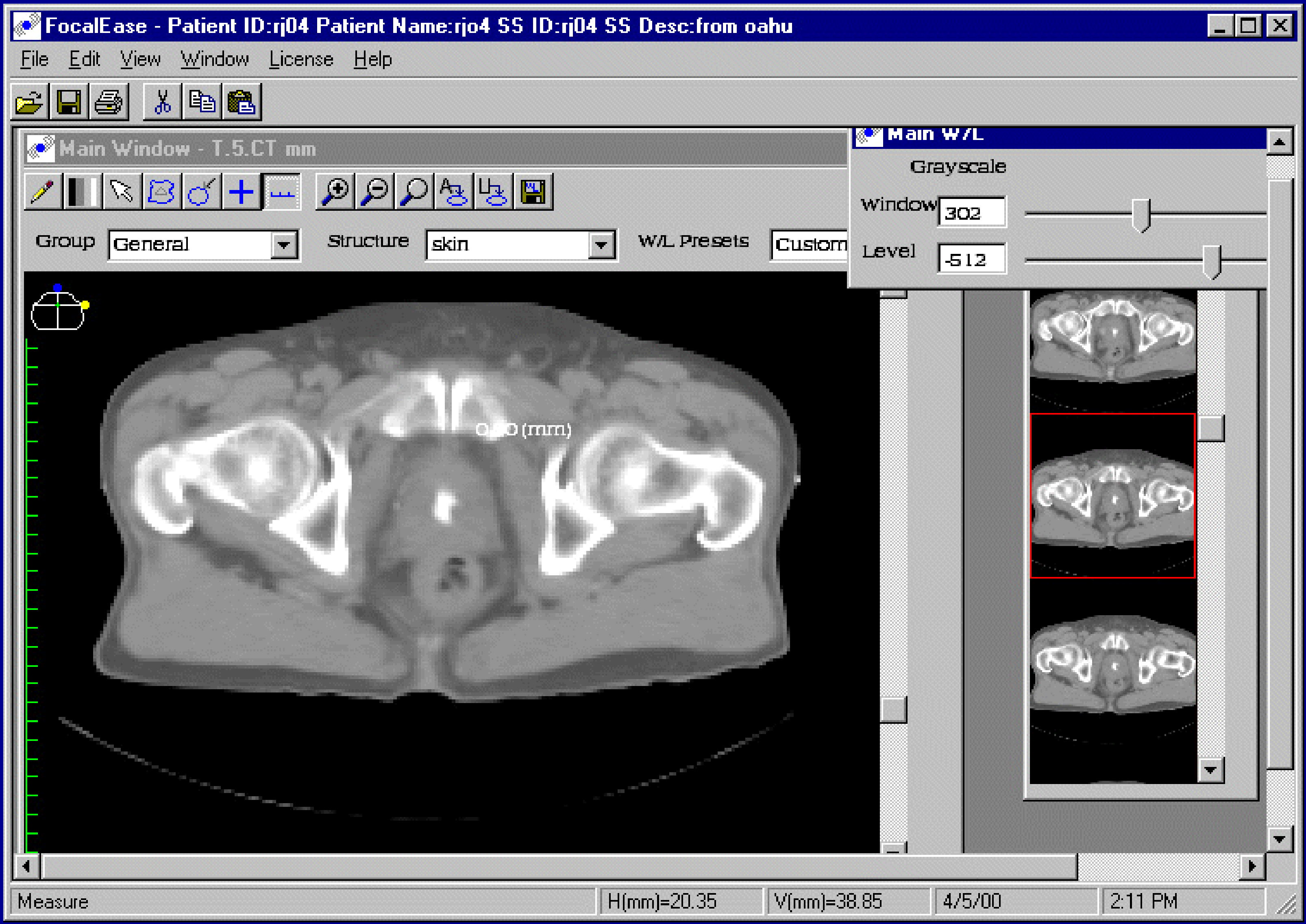
3-D Conformal – 90s



Intensity Modulation – 00s

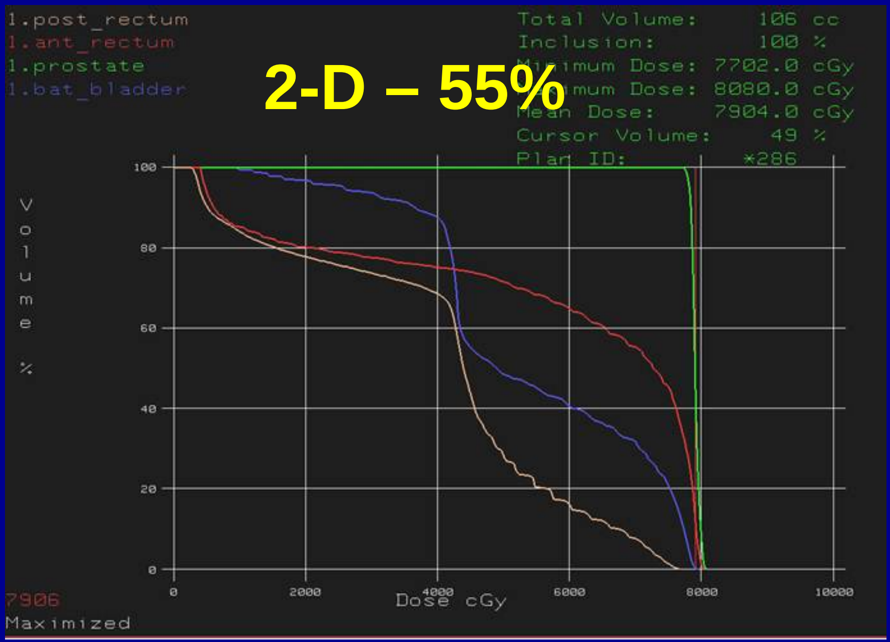


The need for image-guided radiation therapy

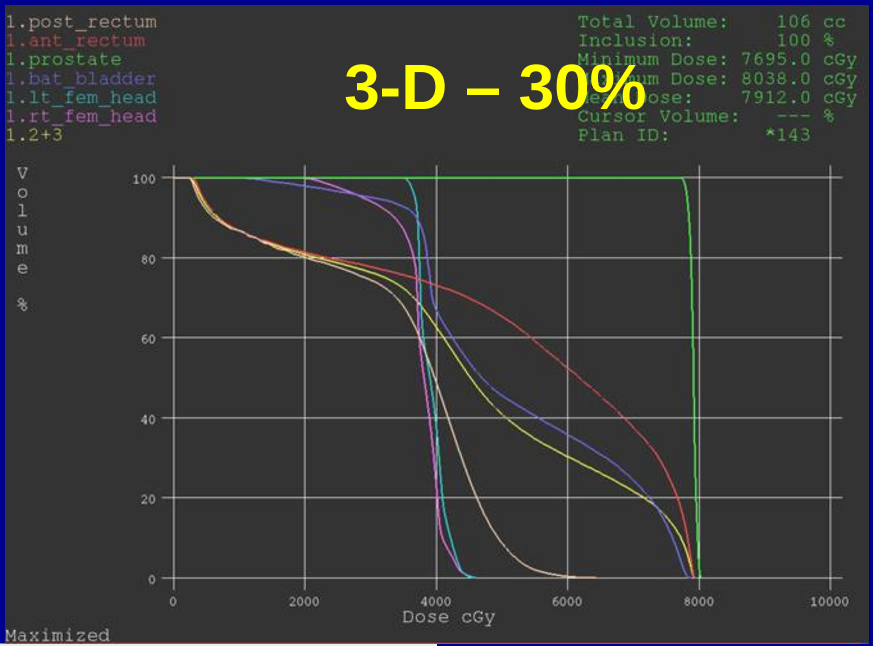


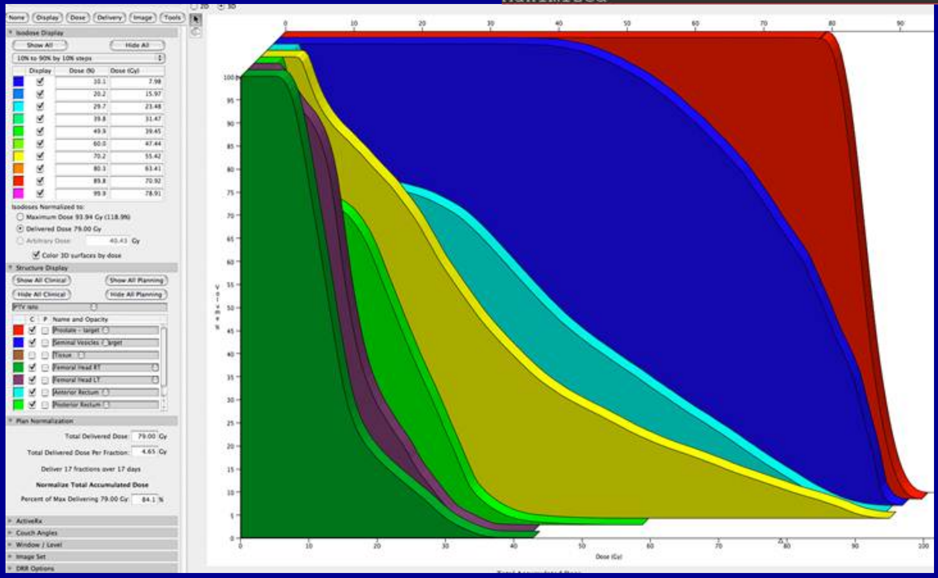
Comparative DVHs:
Volume of anterior rectum >70Gy

2-D – 55%



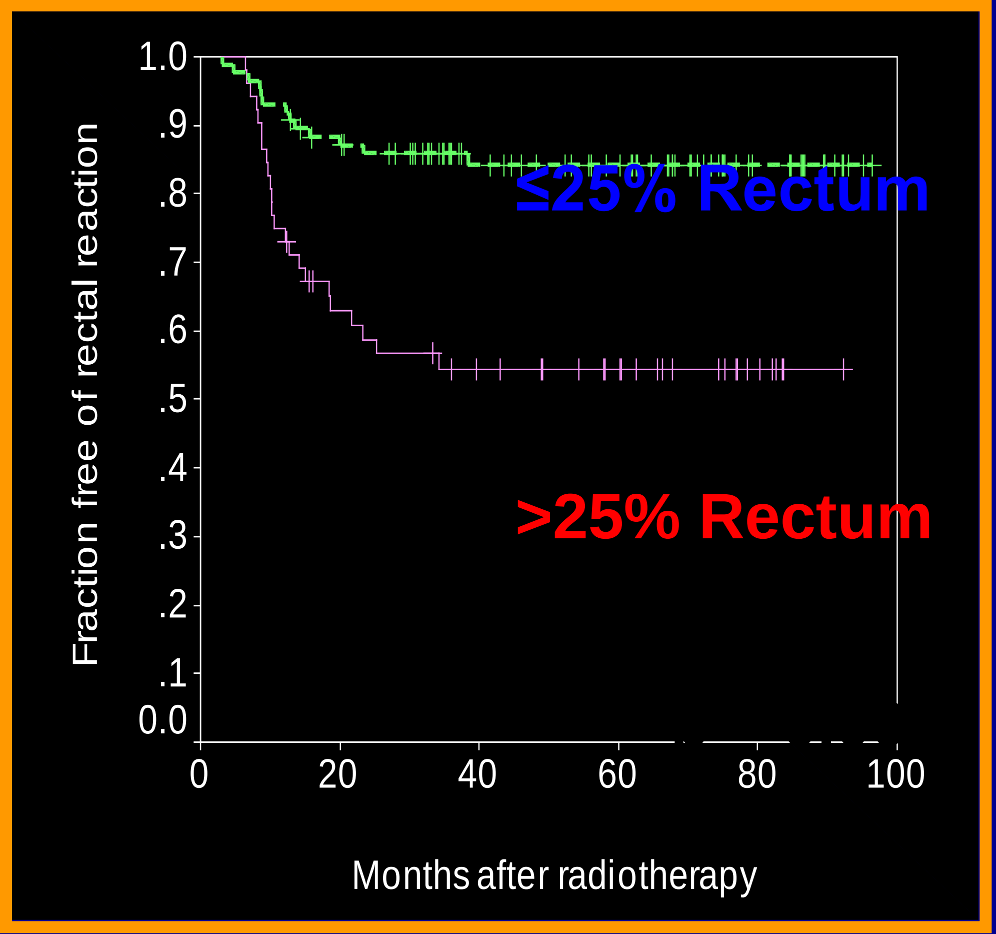
3-D – 30%





IMRT – <10%

MDACC 78 Gy Arm Grade ≥2 late rectal toxicity: Subdivided by percent rectum treated to ≥70 Gy



6 yr Rectal toxicity (2+)

≤25%: 16%

>25%: 46%

Kuban DA, et al. *Int J Radiat Oncol Biol Phys* 2008; 70: 67-74.

Conformal Radiation in Localized Prostate Cancer

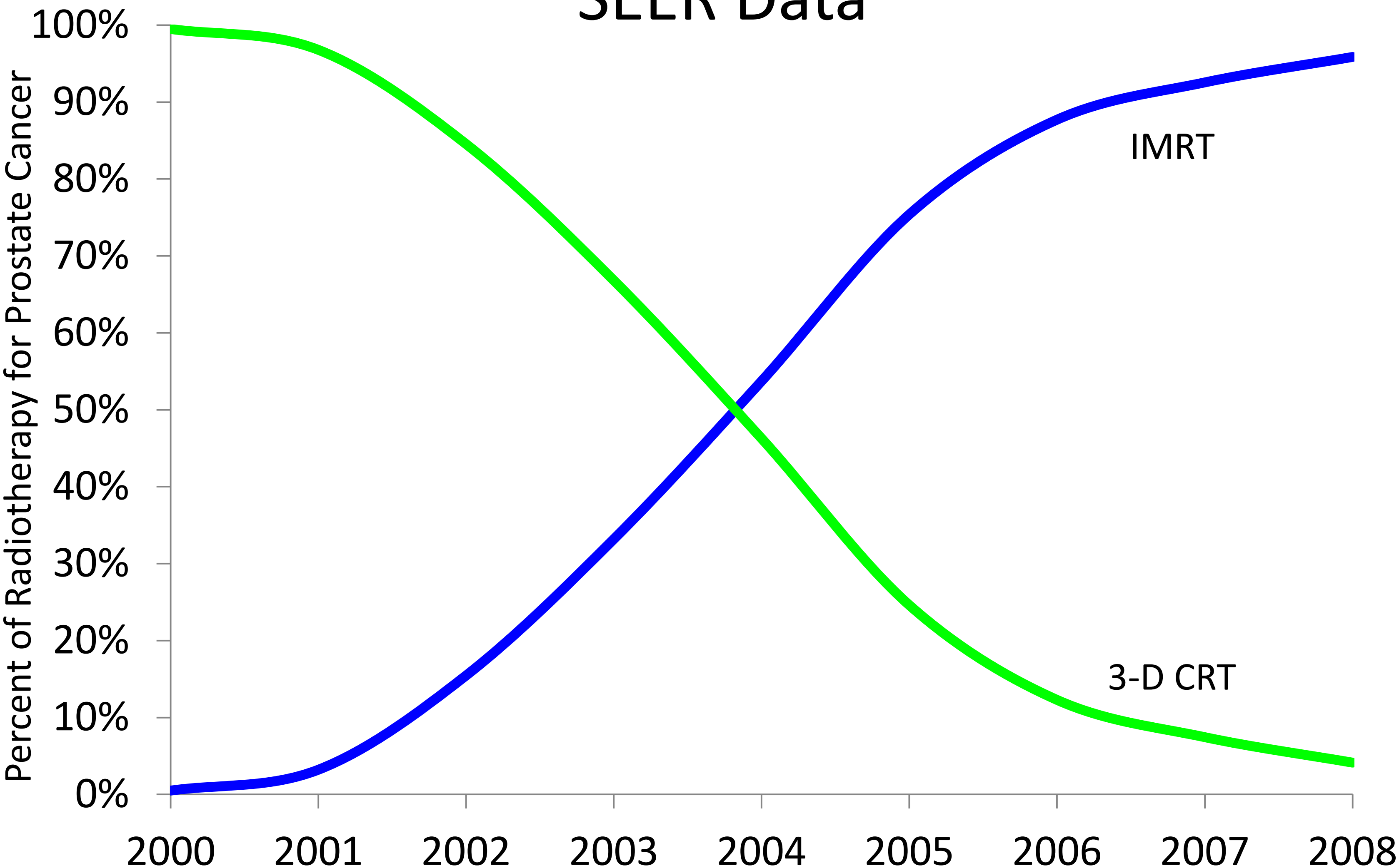
Royal Marsden Randomized Trial 1999

Proctitis

	Grade 1	Grade 2
Conformal (3D)	37%	5%
Conventional (2D)	56%	15%

Dearnaley DP, et al. *Lancet* 1999; 353: 267-272.

Utilization of IMRT for localized Prostate Cancer: SEER Data



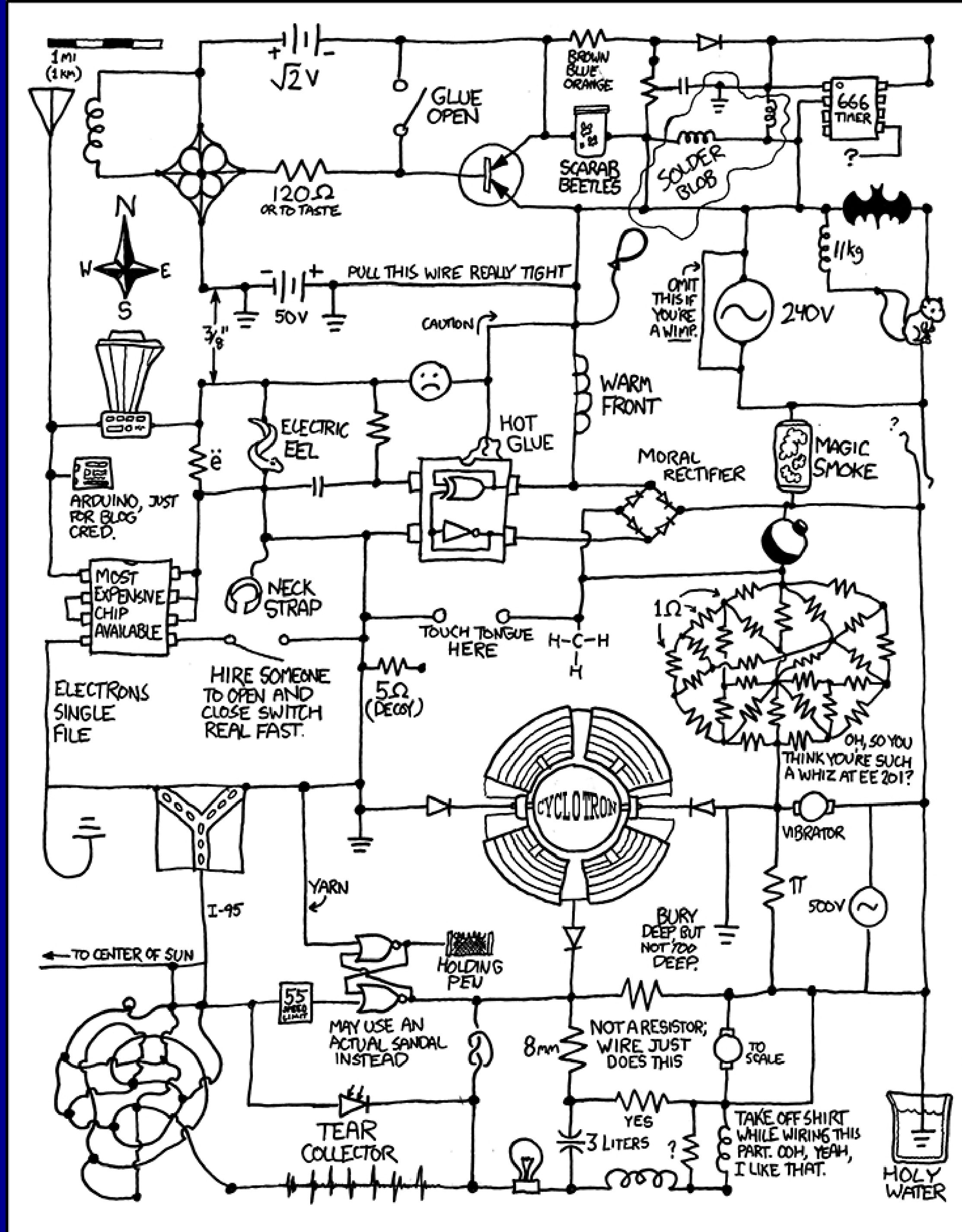
Sheets, Goldin, Meyer, et al., JAMA 2012

And now…….proton therapy

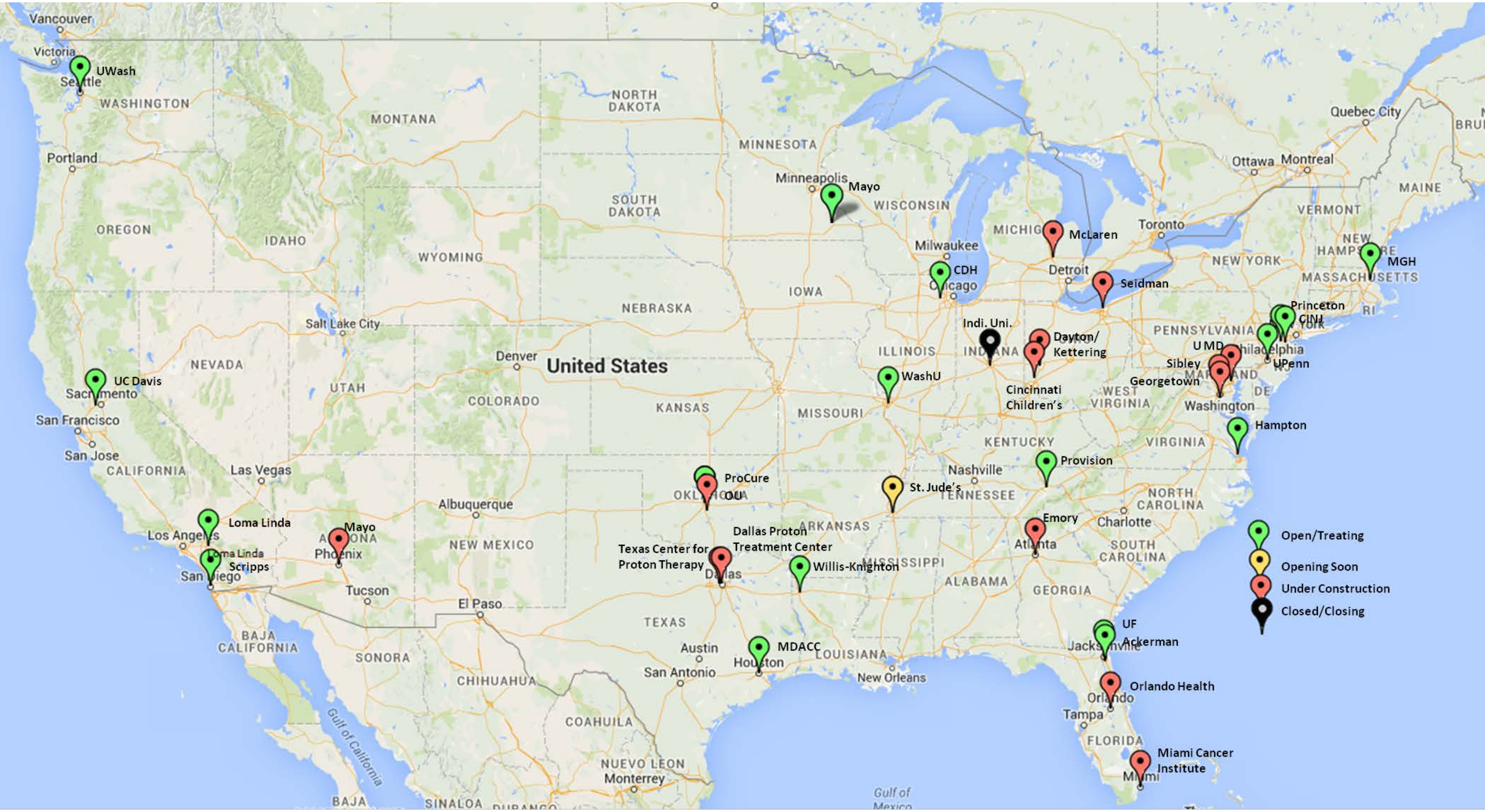
Aims:

?Better tumor eradication through higher doses

?Reduced morbidity


1 MI (1 KM)
√2 V
GLUE OPEN
BROWN BLUE ORANGE
666 TIMER
?
SCARAB BEETLES
SOLDER BLOB
120Ω OR TO TASTE
N
W
E
S
PULL THIS WIRE REALLY TIGHT
50V
3/8"
CAUTION
OMIT THIS IF YOU'RE A WIMP.
240V
1/kg
WARM FRONT
ELECTRIC EEL
HOT GLUE
MORAL RECTIFIER
MAGIC SMOKE
ë
ARDUINO, JUST FOR BLOG CRED.
MOST EXPENSIVE CHIP AVAILABLE
NECK STRAP
TOUCH TONGUE HERE
H-C-H
H
1Ω
ELECTRONS SINGLE FILE
HIRE SOMEONE TO OPEN AND CLOSE SWITCH REAL FAST.
5Ω (DECOY)
OH, SO YOU THINK YOU'RE SUCH A WHIZ AT EE 201?
CYCLOTRON
VIBRATOR
π
500V
BURY DEEP BUT NOT TOO DEEP.
YARN
I-95
TO CENTER OF SUN
HOLDING PEN
55 SPEED LIMIT
MAY USE AN ACTUAL SANDAL INSTEAD
8mm
NOT A RESISTOR; WIRE JUST DOES THIS
TO SCALE
YES
3 LITERS
?
TAKE OFF SHIRT WHILE WIRING THIS PART. OOH, YEAH, I LIKE THAT.
TEAR COLLECTOR
HOLY WATER

www.xkcd.com



UWash
UC Davis
Loma Linda
Loma Linda
Scripps
Mayo
Mayo
ProCure
OU
Texas Center for Proton Therapy
Dallas Proton Treatment Center
Willis-Knighton
MDACC
St. Jude's
WashU
CDH
Indi. Uni.
McLaren
Seidman
Dayton/ Kettering
Cincinnati Children's
Provision
Emory
UF
Ackerman
Orlando Health
Miami Cancer Institute
Hampton
Georgetown
Sibley
U MD
UPenn
Princeton
CINJ
MGH
United States
Open/Treating
Opening Soon
Under Construction
Closed/Closing

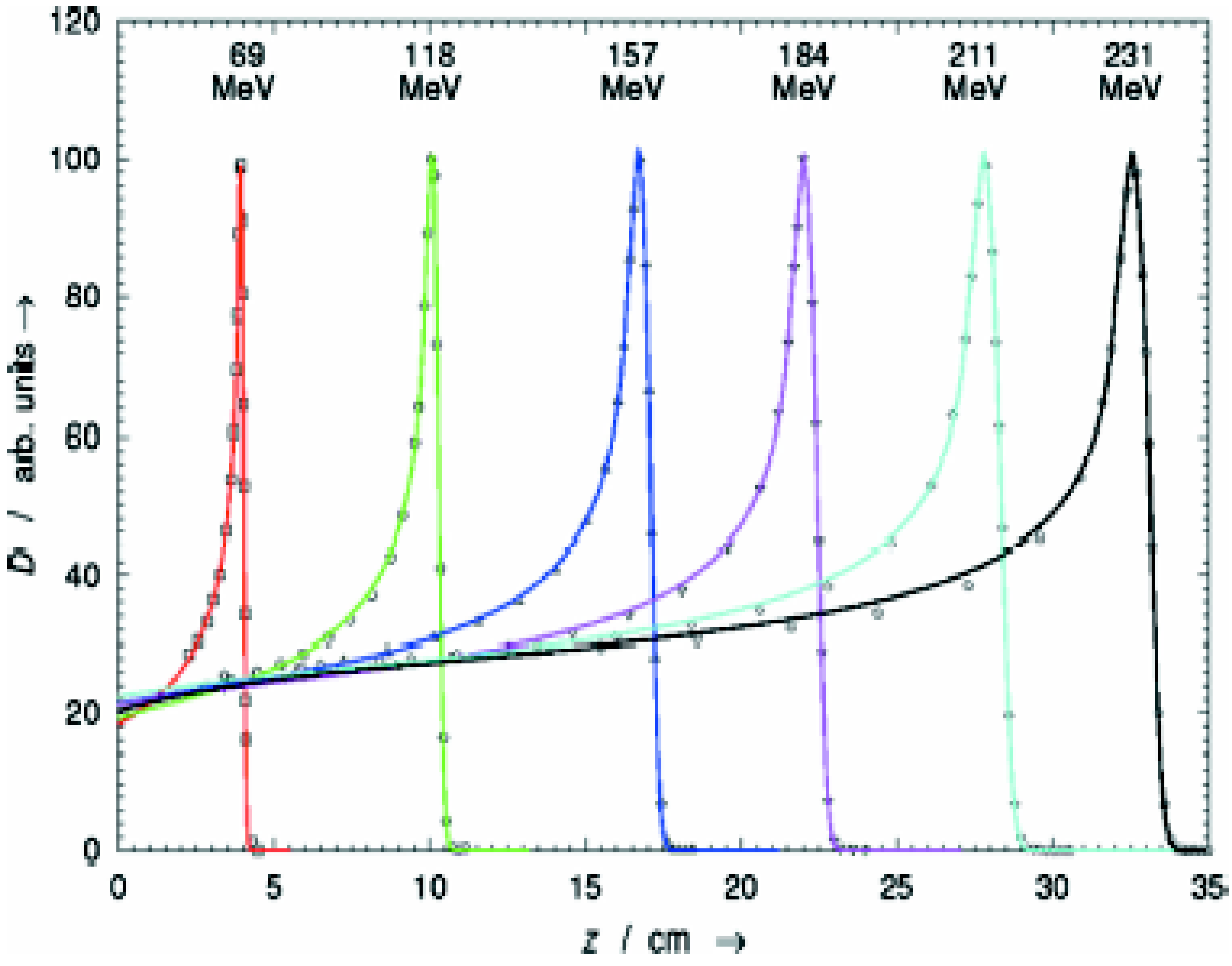
Proton Beam Therapy

- The physics
- The clinical potential

Proton Beam Therapy

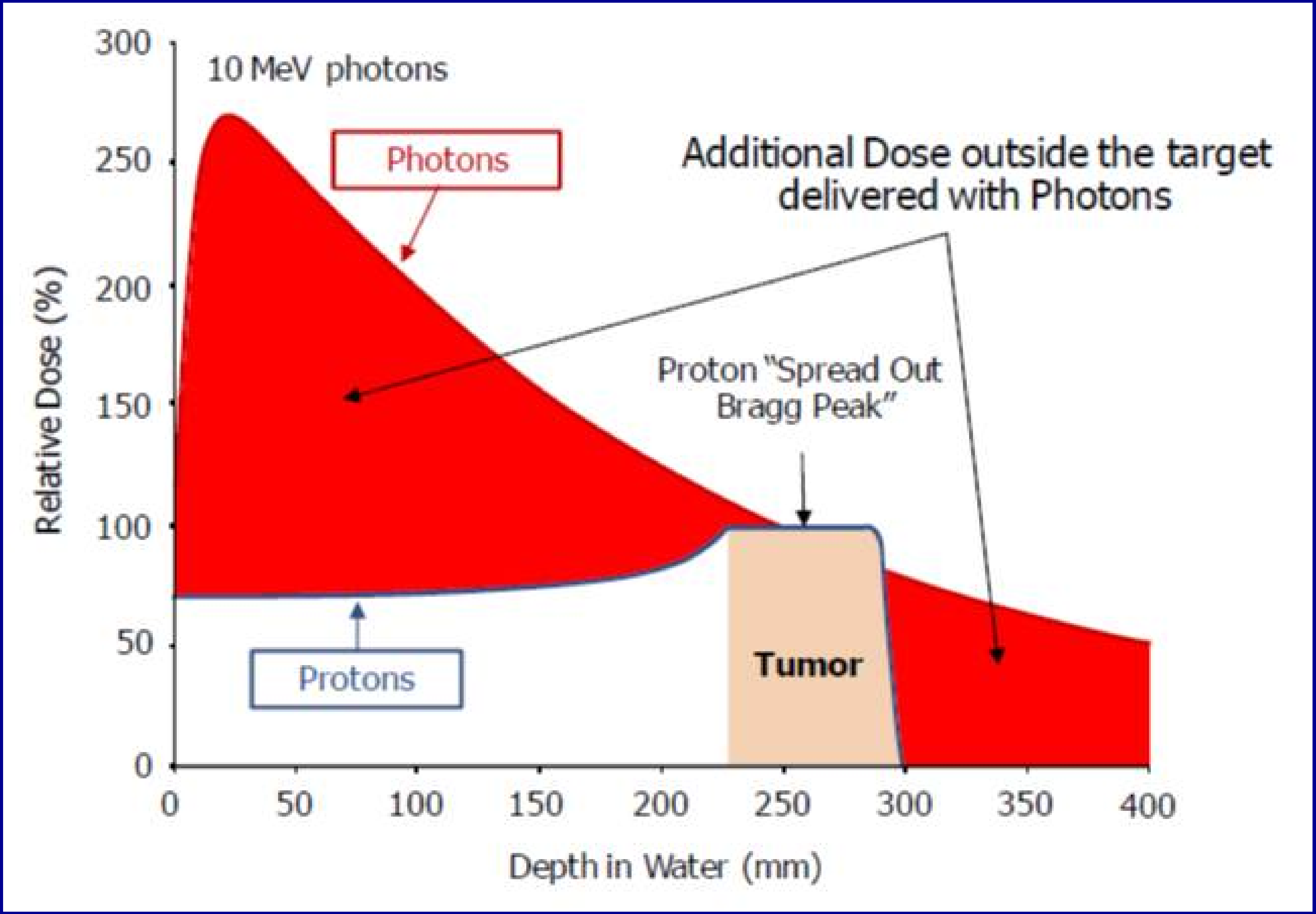
- The physics
- The clinical potential

Pristine Bragg Peaks of Selected Energies



Courtesy of
H. Kooy, Ph.D.

Radiation deposition in tissue for photons vs protons

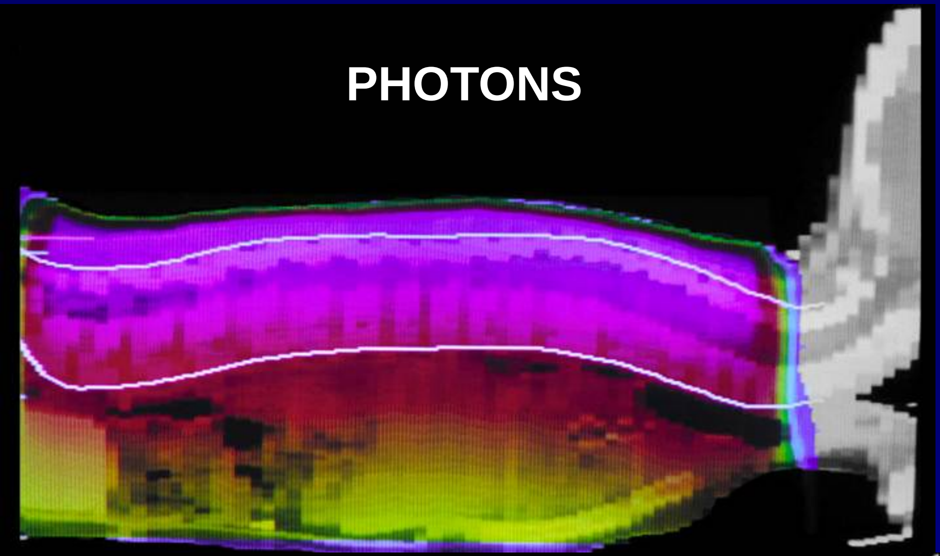


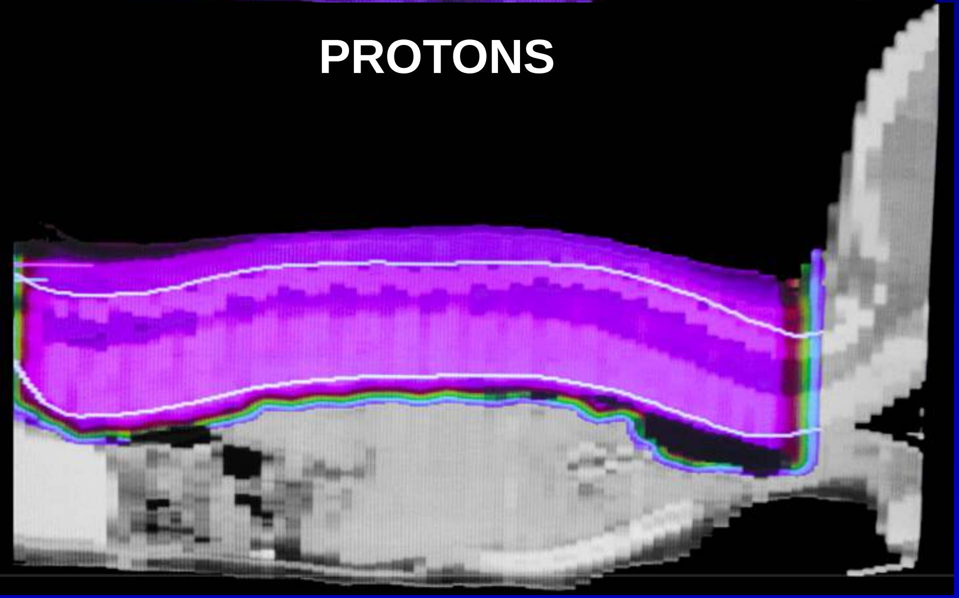
Wilson RR . *Radiology* 1946; 47, 487-491.

Proton Beam Therapy

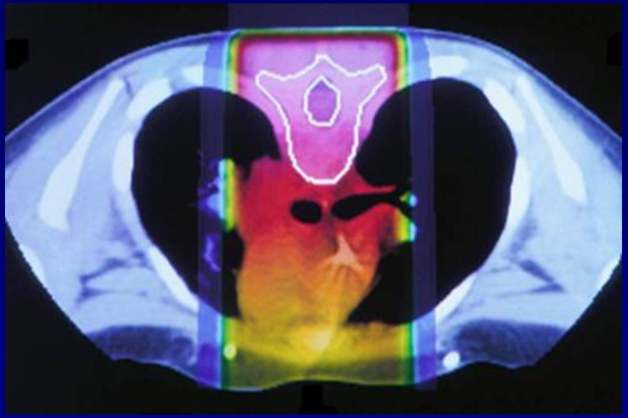
- The physics
- The clinical potential

MEDULLOBLASTOMA

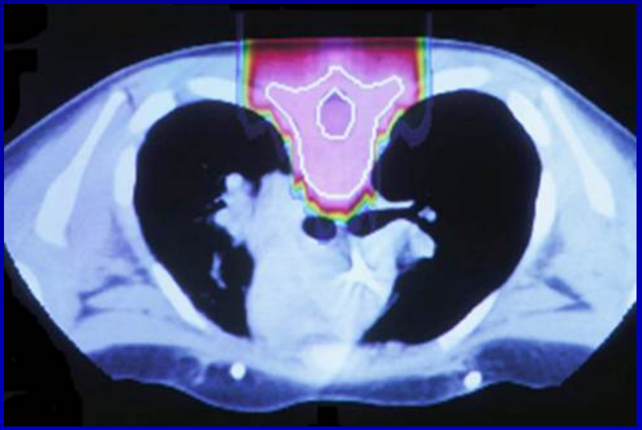




PHOTONS

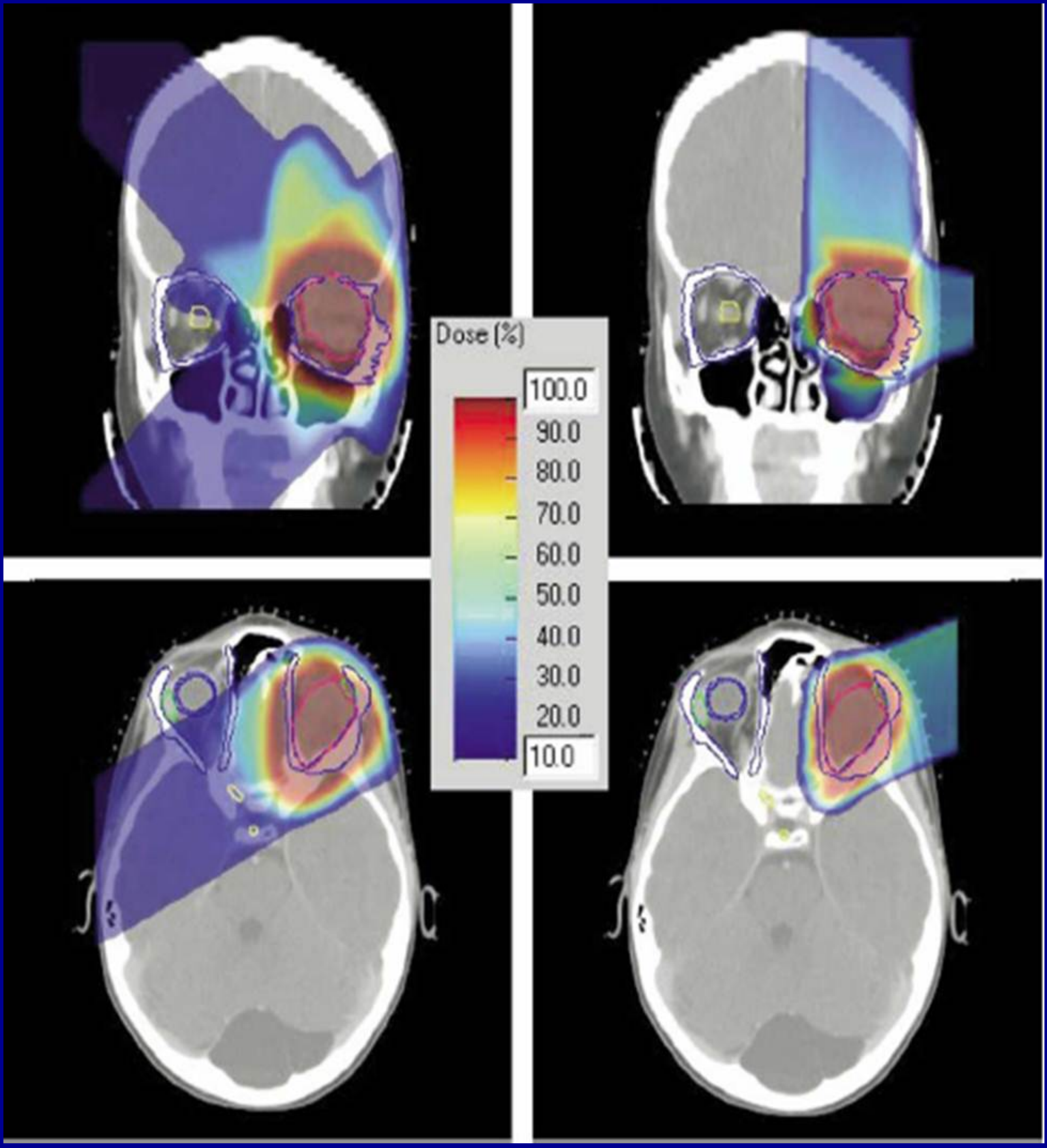


PROTONS



Courtesy T. Yock, N. Tarbell, J. Adams

Orbital Rhabdomyosarcoma



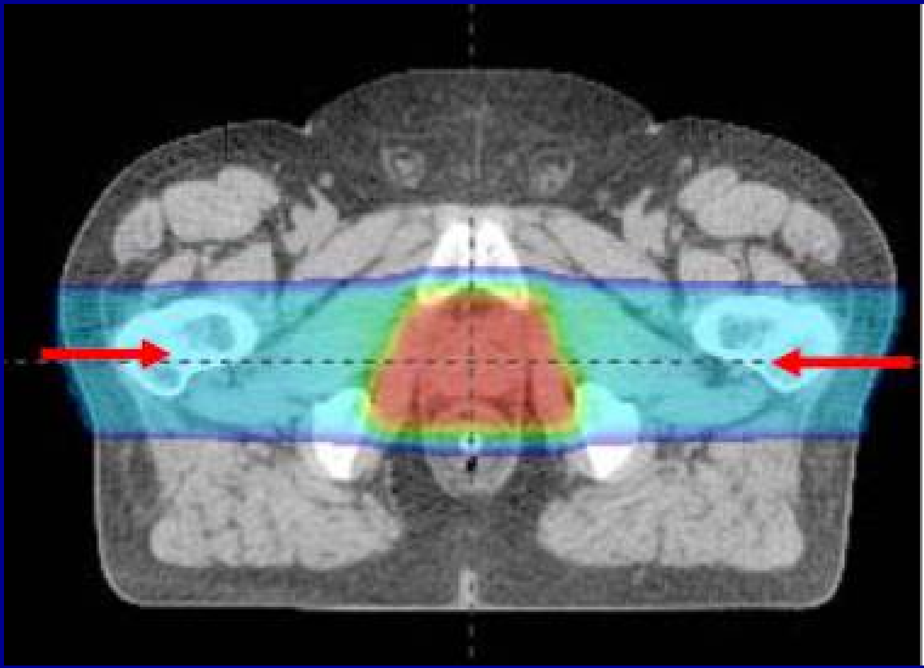
Courtesy T. Yock, N. Tarbell, J. Adams

Photon

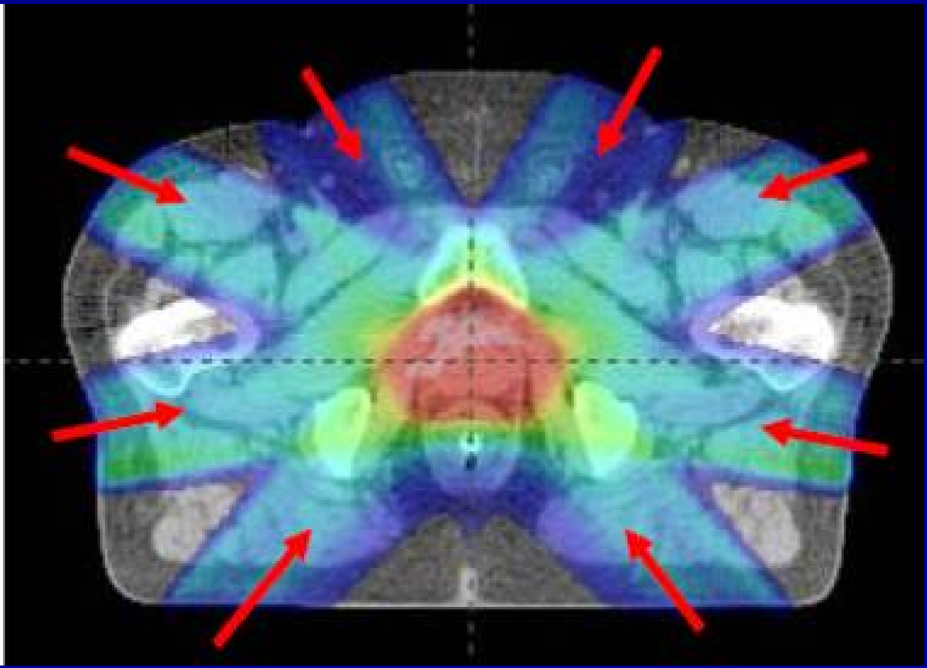
Proton

Prostate

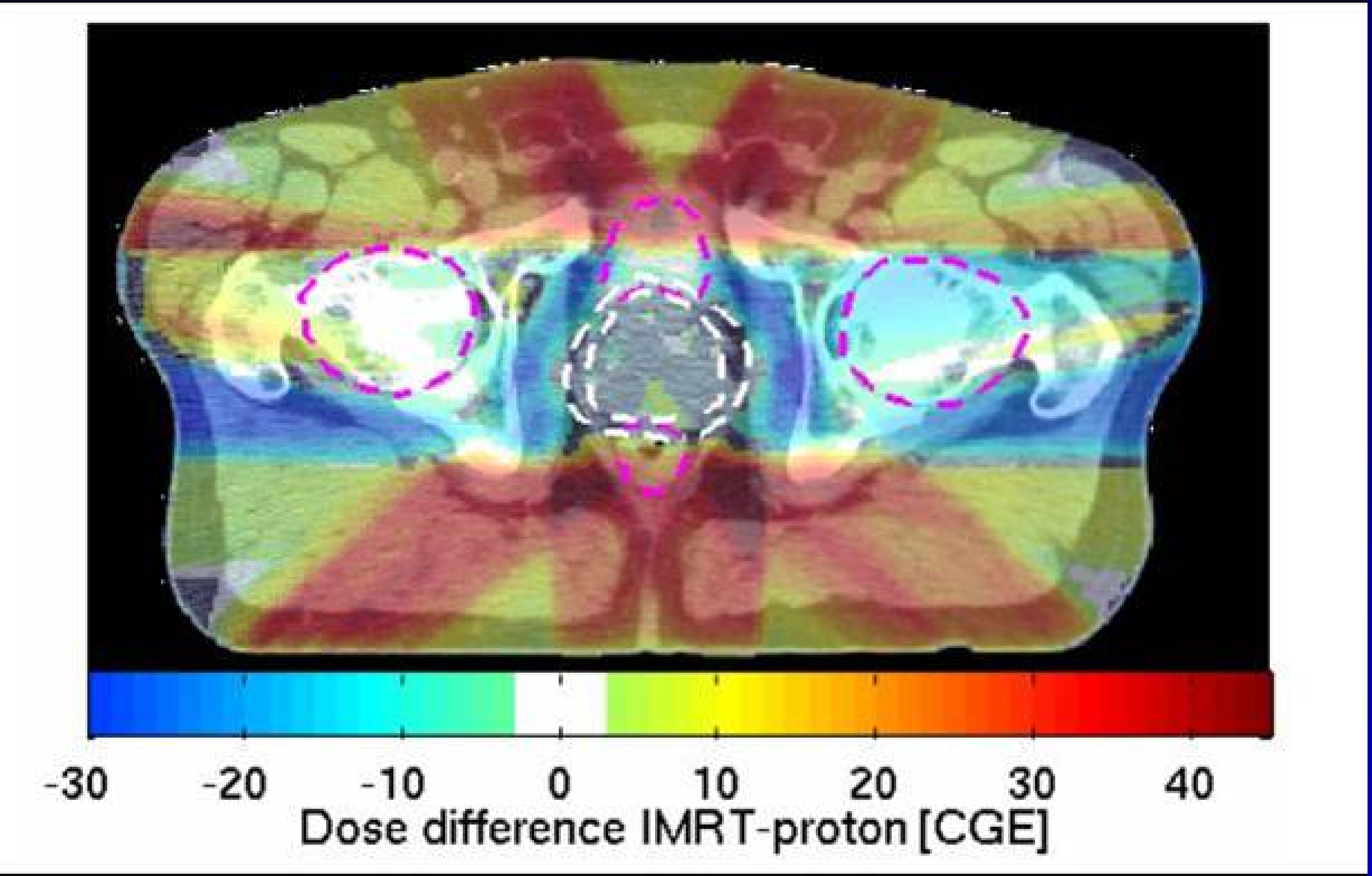
Protons



IMRT

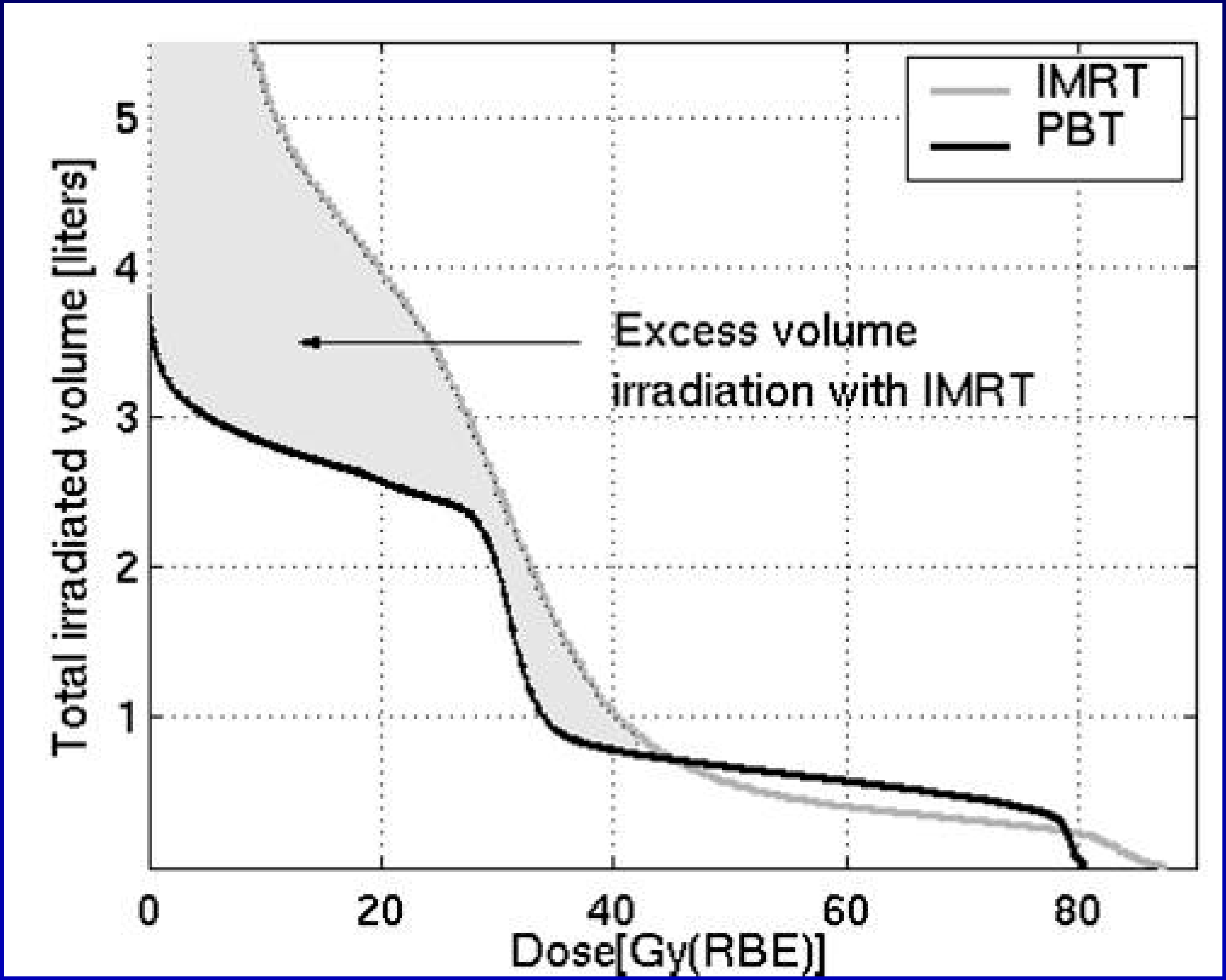


Excess Radiation Dose: IMRT vs protons



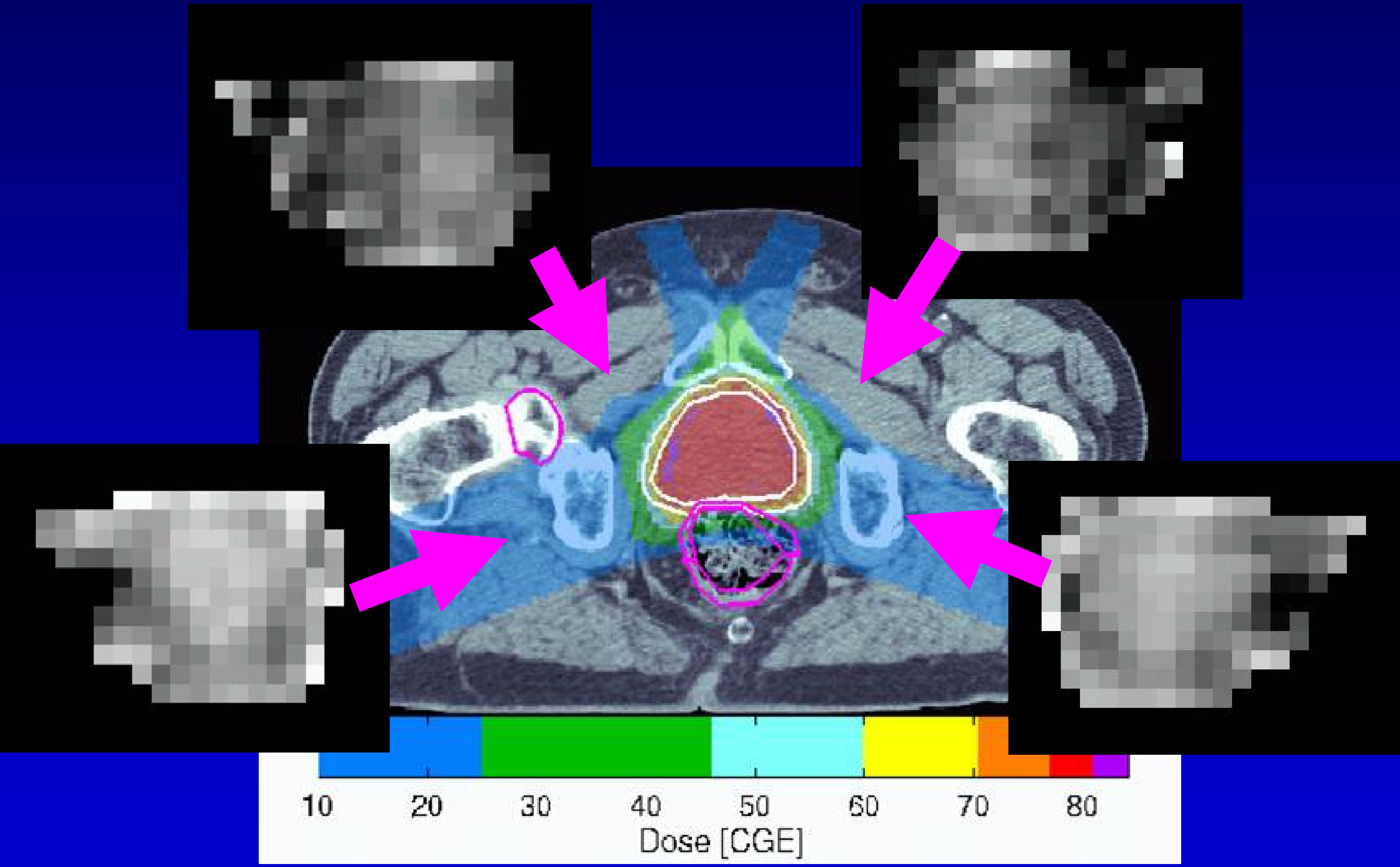
Efstathiou et al. *The Cancer Journal* 2009;15:312-8.

Whole body radiation dose: marked reduction in integral dose

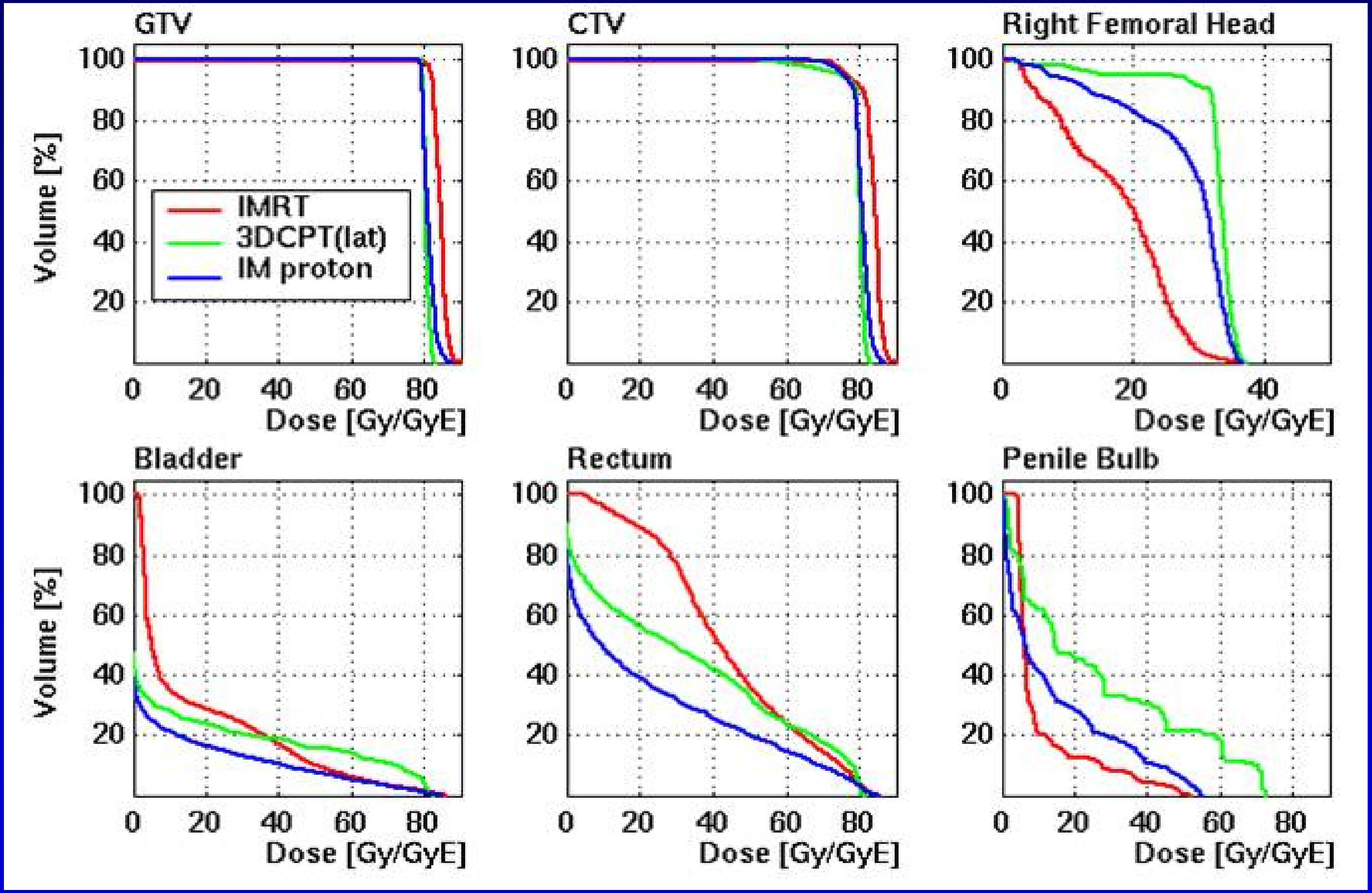


Courtesy of A. Trofimov

Beam Scanning Technology

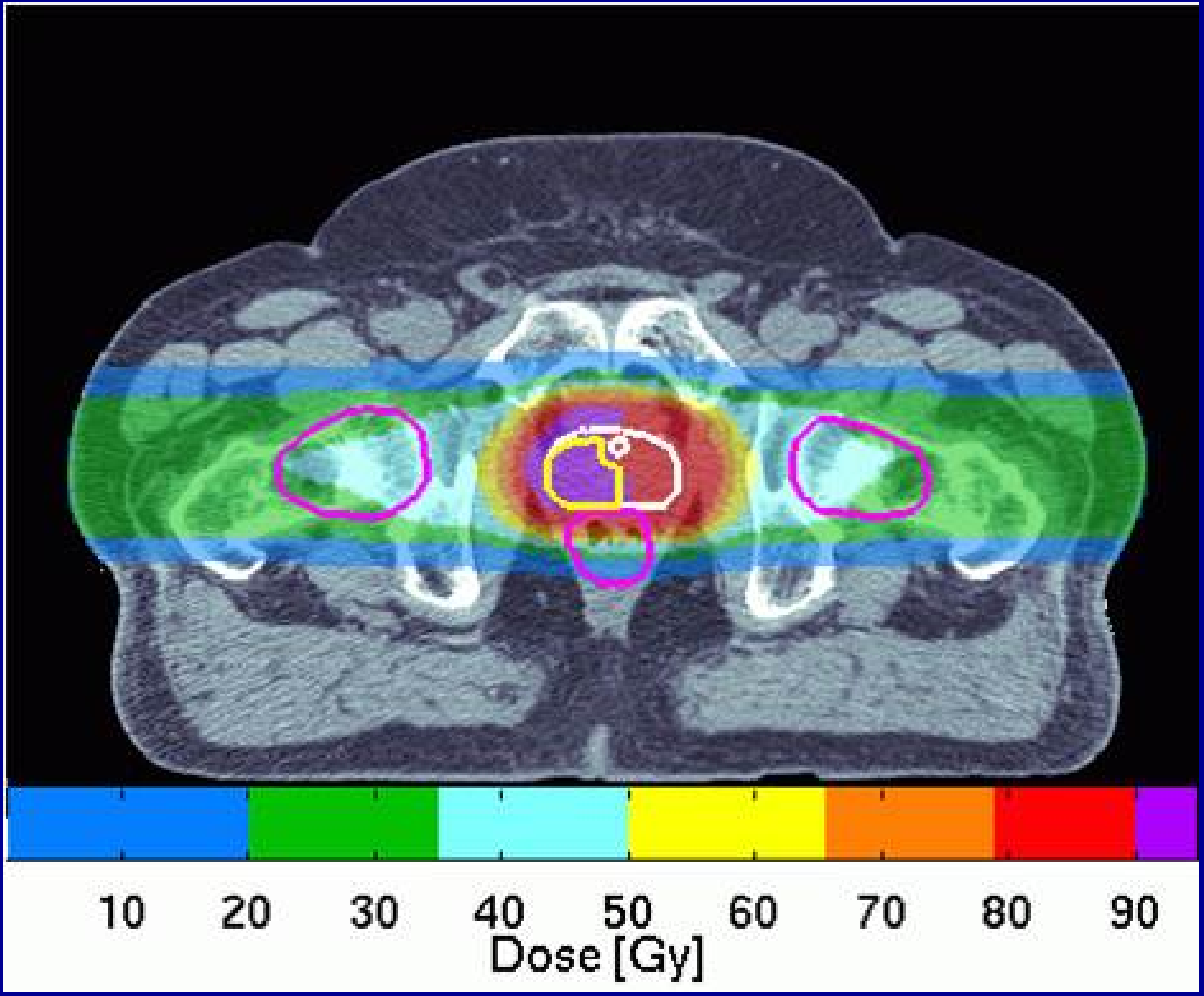


Comparative DVHs for IMRT, Protons, and IMPT



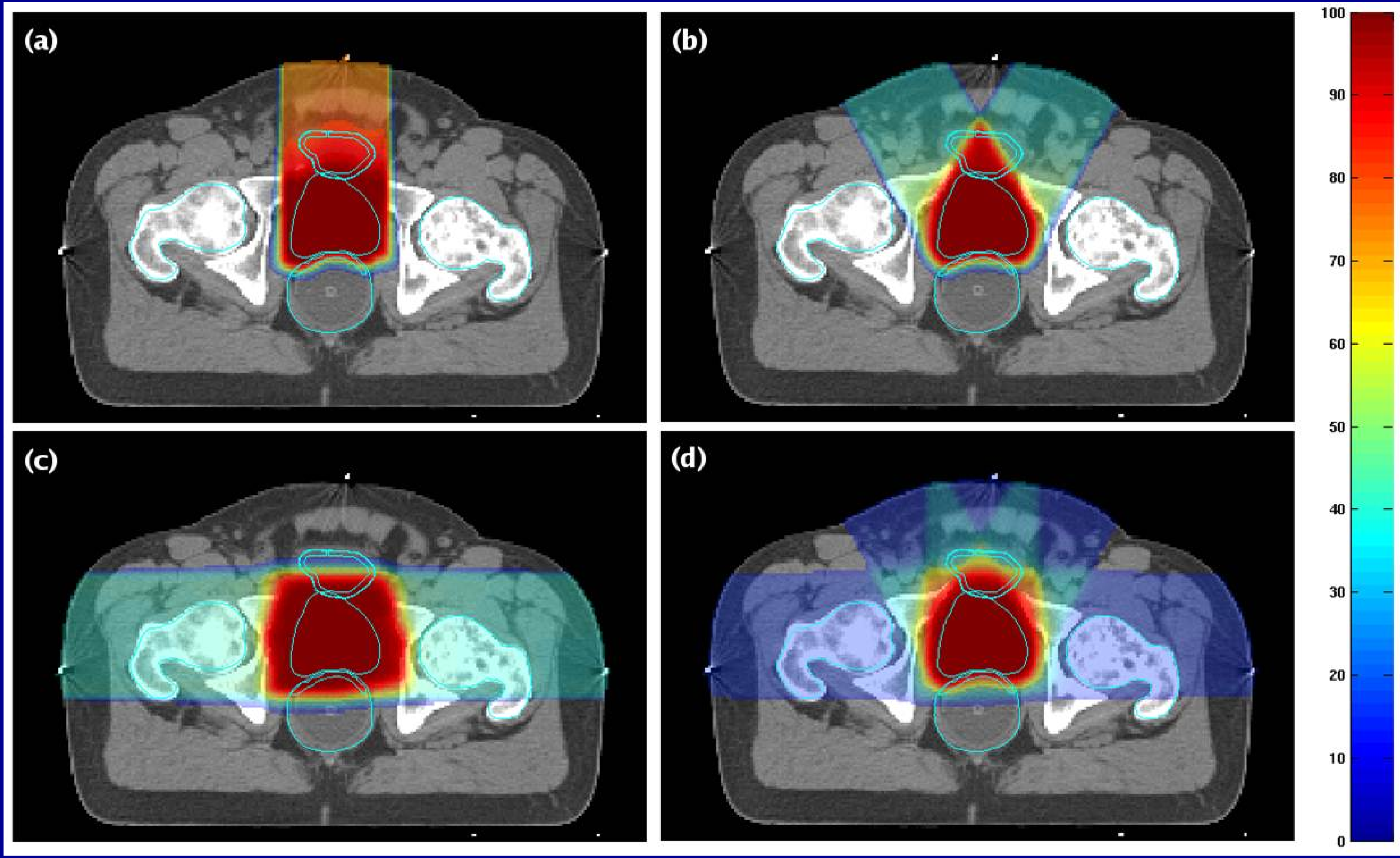
Trofimov A et al. *Int J Radiat Oncol Biol Phys 2007;* 69: 444-453.

Future Possibilities: Partial Prostate Boost using IMPT



Efstathiou et al. *The Cancer Journal* 2009;15:312-8.

Future Possibilities: Anterior fields



Tang et al. *Int J Radiat Oncol Biol Phys*. 2011.

Patient-Reported QOL: Proton beam (Univ of Florida)

Table 3 Patient-reported outcomes according to IPSS and EPIC questionnaires, respectively

	Baseline				4 + Years				
Protocol	No. of patients	Med	Min	Max	No. of patients	Med	Min	Max	*P* value
IPSS									
PR-01	89	8	0	23	61	7	0	27	.7
PR-02	82	7	0	25	56	6	0	20	.74
PR-03	40	9	0	24	20	7	1	20	.12
Total	211	8	0	25	137	7	0	27	.13
Urinary irritative/obstructive summary									
PR-01	86	88	44	100	62	94	19	100	.2
PR-02	70	94	44	100	56	94	19	100	.98
PR-03	33	88	44	100	20	88	44	100	.21
Total	189	94	44	100	138	94	19	100	.59
Urinary Incontinence Summary*									
PR-01	82	100	31	100	63	100	23	100	.21
PR-02	70	100	46	100	55	100	31	100	.71
PR-03	34	100	58	100	23	100	15	100	.16
Total	186	100	31	100	141	100	15	100	.10
Bowel summary									
PR-01	86	100	50	100	63	96	58	100	.002
PR-02	72	96	46	100	55	96	50	100	.31
PR-03	38	96	58	100	20	95	42	100	.22
Total	196	96	46	100	138	96	42	100	<.0001

Mendenhall et al., IJROBP 2014

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

- Despite the theoretical advantages of proton therapy, studies have yet to prove a clear clinical benefit to proton therapy compared to IMRT

Men'sHealth

“The Magic Bullet for Prostate Cancer” (2011)

“The Magic Bullet Falls Short” (2012)

SEER-Medicare studies question proton therapy for prostate cancer

Sheets et al., JAMA 2012; Kim et al., Eur Urol 2011

SEER-Medicare Studies

- Treatment dose data?
- Target margins?
- Use of image guidance?
- Differentiates proton from mixed proton/photon?
- Includes >1 proton center?
- Differentiate screening colonoscopies from diagnostic colonoscopies?
- Includes patient-reported outcomes?
- Potential misclassification bias?
- Potential confounding by unrecorded variables?
- Lingering questions?

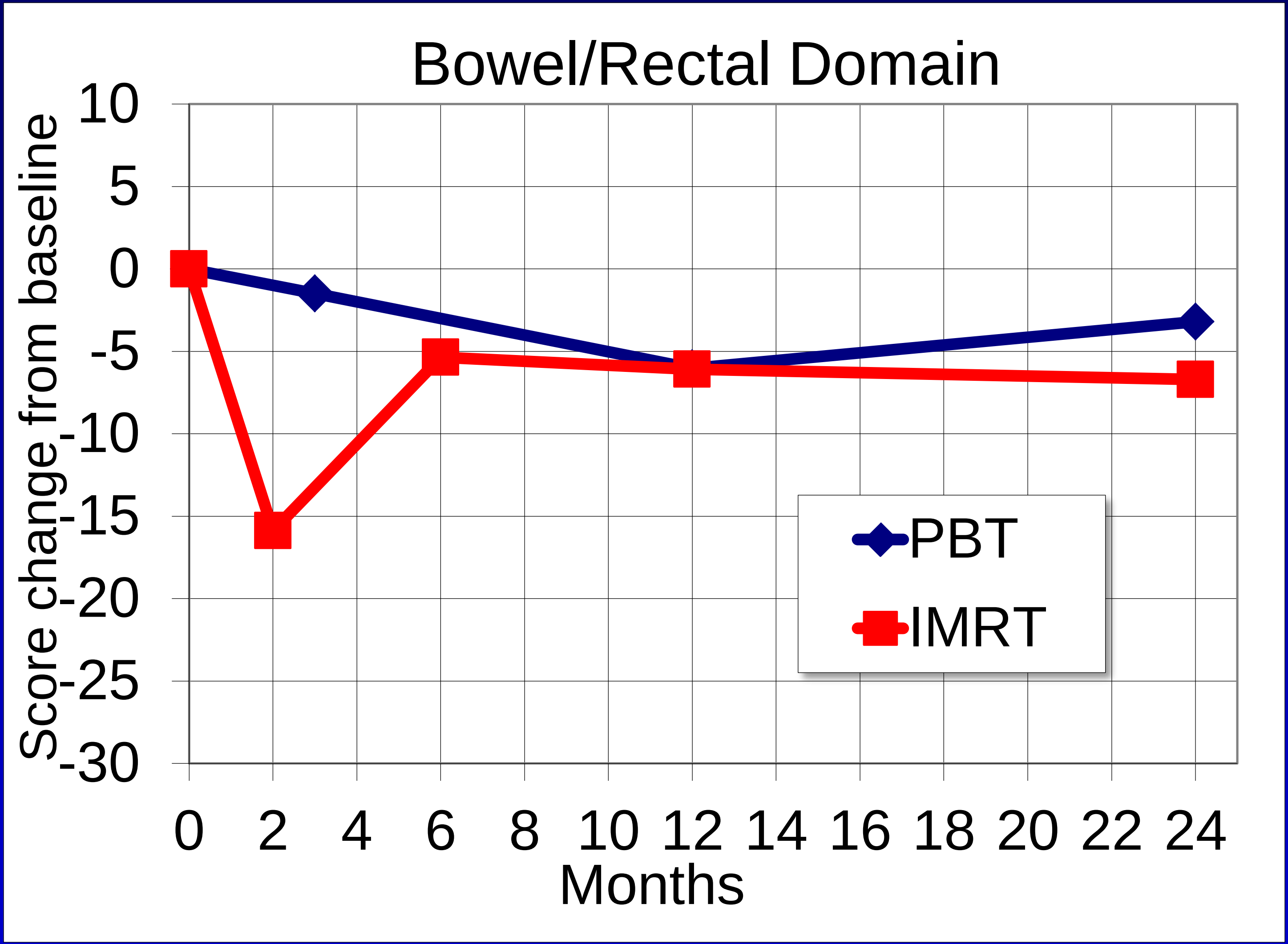
Sheets et al., JAMA 2012; Kim et al., Eur Urol 2011

Medicare Studies

Complications category	6-month toxicity IMRT, n = 842, No. (%)	PRT, n = 421, No. (%)	OR† (95% CI)	*P*‡
Genitourinary	80 (9.5)	25 (5.9)	0.60 (0.38 to 0.96)	.03
Gastrointestinal	30 (3.6)	12 (2.9)	0.84 (0.42 to 1.66)	.61
Other	21 (2.5)	<11 (<2.6)§	0.69 (0.29 to 1.66)	.41

Yu et al., JNCI 2012

Patient Reported Bowel Toxicity

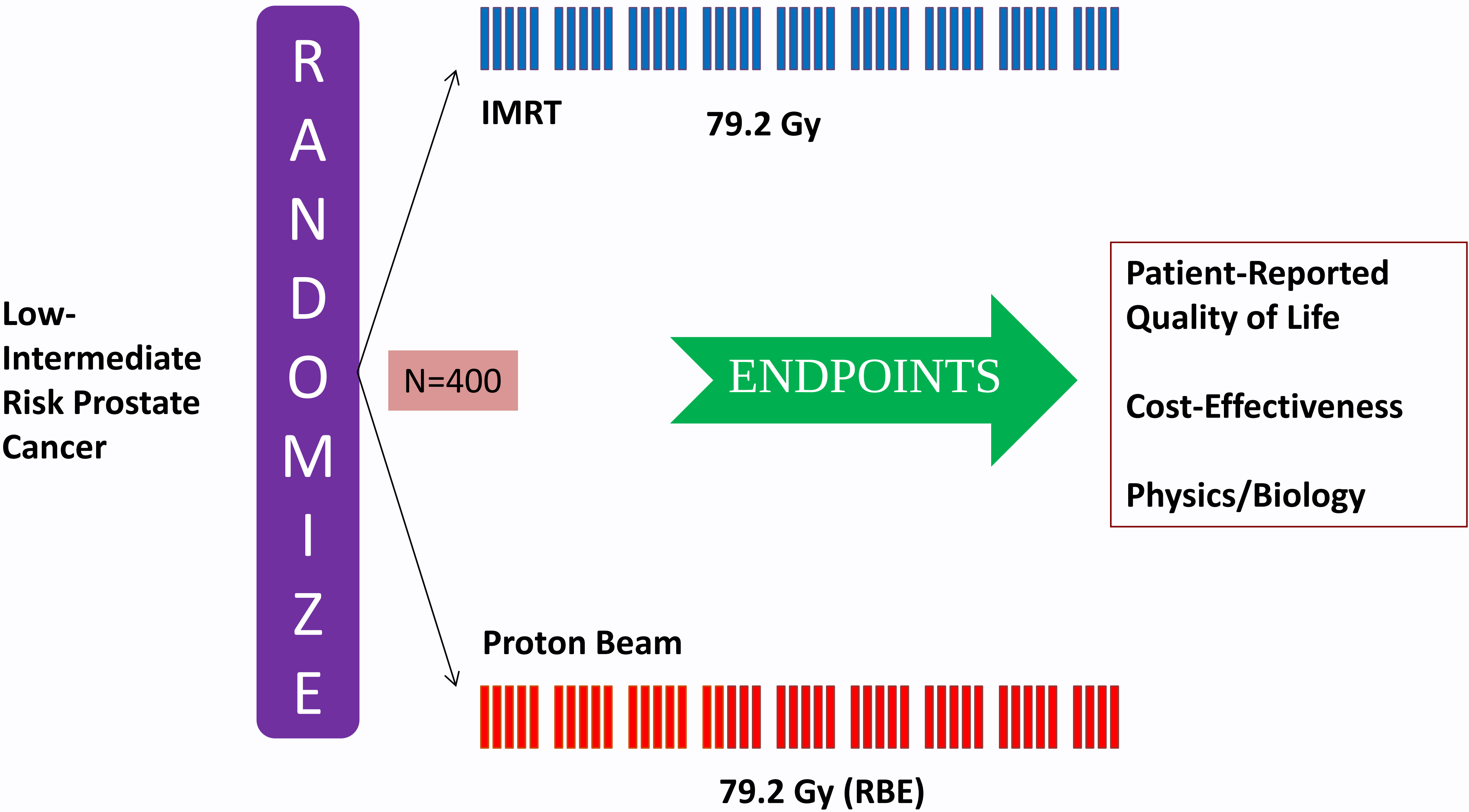


Gray et al. Cancer 2013

Proton Therapy

	Prostate	Breast	Lung
Randomized trial (RCT)	• PARTIQOL RCT	• RADCOMP Pragmatic RCT	• RTOG 1308 RCT
Sponsor	National Cancer Institute; MGH 1811	pcori	National Cancer Institute; NRG Oncology Advancing Research. Improving Lives.™
Primary endpoint	• Patient reported bowel fxn	• Major CV events and relapse	• Survival
Patient-centric?	• ++++	• ++++	• ++++
Payer-centric?	• +++	• ++++	• +++++
Timeline	• > 5 years	• > 10 years	• > 5 years

PARTIQoL RCT



clinicaltrials.gov identifier: NCT01617161

PARTIQoL RCT Update

(Prostate Advanced Radiation Technologies Investigating Quality of Life)

<u>Primary Objective:</u> **Compare reduction in *mean EPIC bowel scores* for men with low or intermediate risk PCa treated with PBT versus IMRT at 24 months following treatment *(where higher scores represent better outcomes).***
Hypothesis: given the physical characteristics of protons (no exit dose), PBT will result in improved patient reported outcomes for a given radiation dose

<u>**Secondary Objectives**</u>

1. **Assess the effectiveness of PBT versus IMRT in terms of disease-specific quality of life as measured by patient-reported outcomes, perceptions of care and adverse events**
2. **Assess the cost-effectiveness of PBT versus IMRT under current conditions and model future cost-effectiveness for alternative treatment delivery and cost scenarios**
3. **Develop predictive models to examine the associations between selected metrics of individual radiation dose distributions (including both the planned, and delivered doses estimated based on serial imaging) and patient reported bowel, urinary, and erectile function**
4. **Identify and evaluate biomarkers of prostate cancer behavior and response to radiotherapy**
5. **Assess longer-term rates of disease-specific and overall survival as well as development of late effects such as second cancers.**

NATIONAL CANCER INSTITUTE®

PARTIQoL RCT Update
(Prostate Advanced Radiation Technologies Investigating Quality of Life)

- **107 patients randomized as of July 20th, 2015**
- **Trial fully activated at:**
  - **MGH, UPenn, MDACC, Washington University (St. Louis), Northwestern Medicine/Chicago Proton Center, Princeton Radiation Oncology**
- **Soon to be activated at:**
  - **MSKCC, University of Washington (Seattle), Provision Center for Proton Therapy (Knoxville), Rutgers/Cancer Institute of New Jersey**
- **In the process of adding (when open):**
  - **Mayo (Rochester/Phoenix), Maryland**

PARTIQoL RCT Update

(Prostate Advanced Radiation Technologies Investigating Quality of Life)

- Strong collaborations have been developed with sites that enroll, and with the Advanced Technology Consortium for support of treatment plan review and archiving

- Other efforts have focused on patient and provider education and recruitment including minority outreach, quality assurance and optimization of treatment delivery

- Majority (96%) of patients consented to release of health insurance records and we are collecting direct medical costs, insurance claims and healthcare utilization data

PARTIQoL RCT Update

(Prostate Advanced Radiation Technologies Investigating Quality of Life)

- Factors influencing accrual:
  - Increased use of other management options
  - 36% of eligible patients randomized
    - 50% elect protons, 5% elect IMRT
  - 29 eligible patients willing to be randomized had coverage denied for protons

- The three most common insurers are currently covering 76% of the enrolled patients: Medicare (44%), Blue Cross Blue Shield (21%), and United (11%)

Blue Cross Blue Shield (BCBS) MA
Medical Policy on Charged-Particle Radiation Therapy

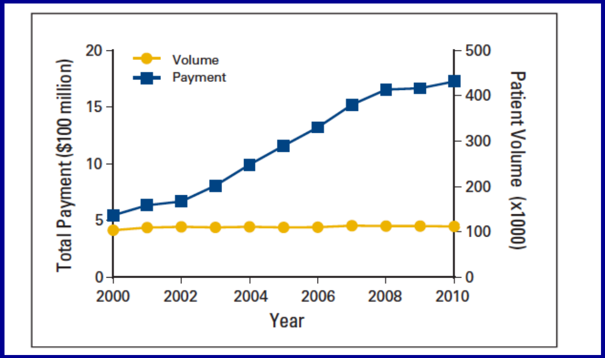
Group 2

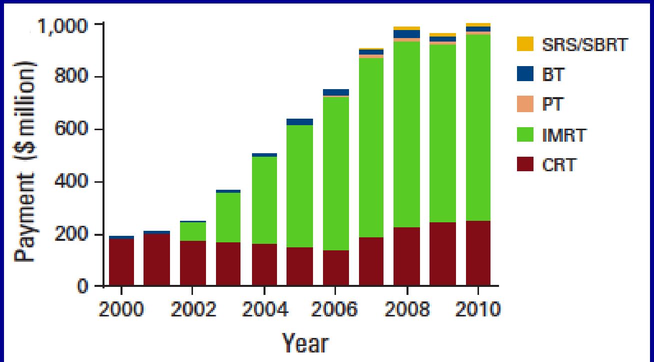
This section defines conditions that are still under investigation and would be covered when part of a clinical trial, registry or both.

- Unresectable lung cancers and upper abdominal/peri-diaphragmatic cancers
- Advanced stage, unresectable pelvic tumors including those with peri-aortic nodes or malignant lesions of the cervix
- Left breast tumors
- Unresectable pancreatic and adrenal tumors
- Skin cancer with macroscopic perineural/cranial nerve invasion of skull base
- Unresectable Malignant lesions of the liver, biliary tract, anal canal and rectum
- Prostate Cancer, Non-Metastatic

Unique Collaboration: Radiation Oncologists' Physician Advisory Council (PAC) and BCBS MA to Optimize Use of Advanced Technology

- RO office-based total patient volume increased by 8% (103,798 to 112,310) between 2000-10, total payments for all billing codes increased from $547 million to $1.7 billion
- IMRT utilization in office-based practices in the US increased from 0% before 2002 to 54% in 2010, accounting for an increase in RO costs of $707 million





X Shen et al: J Oncol Practice, 10 (4): e201-07, 2014

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- **Growing concern about increased use of IMRT without quantifiable metrics in BCBSMA, who then reached out to several MA RO departments, suggesting a cooperative venture to define when the use of IMRT was clinically indicated**
- **MA RO Physicians Advisory Council (PAC) consisting of representatives from 11 academic and private practices met with BCBSMA leadership to reconcile these issues and develop a strategy to better define the use of IMRT**
- **Overarching goal was to achieve evidence-based use of IMRT in daily clinical practice**

L Steingisser et al: J Oncol Practice, 10 (5): e321-26, 2014

Unique Collaboration: Radiation Oncologists' Physician Advisory Council (PAC) and BCBS MA to Optimize Use of Advanced Technology

BCBSMA Leaders

Lee Steingisser, MD

John Fallon, MD, MBA

Eliot Jekowsky, MD

DFCI

Lawrence Schulman, MD

Joseph Jacobson, MD

PAC Members

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Mary Ann Stevenson, MD, PhD

David Wazer, MD

Unique Collaboration: Radiation Oncologists' Physician Advisory Council (PAC) and BCBS MA to Optimize Use of Advanced Technology

- **Initial discussions centered on IMRT approval for specific disease sites**
- **Strong consensus emerged among the PAC radiation oncologists and BCBSMA leaders in support of IMRT as part of localized, primary management of anal, head and neck, prostate, and vulvar malignancies based on available evidence**
- **Further IMRT guidelines were developed by the PAC radiation oncologists based on series of iterative deliberations using current NCI cooperative group normal tissue constraints and Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines**
- **If the established constraints could not be met with conventional radiation, IMRT would be allowed**

L Steingisser et al: J Oncol Practice, 10 (5): e321-26, 2014

Table 1. Normal Tissues Guidelines for the Use of IMRT (15)

Site	Radiotherapy Dose (using three-dimensional techniques)
CNS	
Lens	> 7 Gy
Retinae/globes	> 45 Gy
Optic nerves/chiasm	> 54 GY
Brainstem	> 54 Gy
Head and neck	IMRT covered if any critical structure would receive radiation
Breast	
25% of the heart	> 30 Gy
30% of the ipsilateral lung	> 20 Gy
or	
20% of the combined lung volume	20 Gy
5% of the skin/soft tissue	> 7% of the prescription dose
or	
Primary lesion is medial with >10% of the contralateral breast	> 10 Gy
Thorax/lung	
50% of the heart	> 30 Gy
30% of noncancerous lung	> 20 Gy
1% of the spinal cord	45 Gy
Abdomen	
50% of the heart	> 30 Gy
30% of combined lung	> 20 Gy
or	
Mean lung dose	> 20 Gy
1% of the spinal cord	> 45 Gy
60% of the liver volume	> 30 Gy
or	
Mean liver dose	> 32 Gy
33% of combined renal volume	> 20 Gy (two functional kidneys)
or	
For one functioning kidney and/or renal transplant	IMRT provides a lower dose than three-dimensional techniques
195 cm^3 of small bowel	> 45 Gy
10% of the stomach	45 Gy
or	
5% of the stomach	50 Gy
1% of the femoral head	> 45 Gy
Pelvis (including gynecological oncology; vulva and anus covered for IMRT)	
60% of the rectosigmoid	> 30 Gy
35% of the bladder	> 45 Gy
195 cm^3 of small intestine	> 45 Gy
Lymphoma and sarcoma of the head/neck, retroperitoneum, chest wall/thorax	Guidelines are identical to those listed for head/neck, abdomen, and pelvis
Sarcoma of the extremity	
50% of the contiguous femur cortex	> 50 Gy
Pediatrics	Pediatrics is covered for IMRT

Abbreviation: IMRT, intensity-modulated radiation therapy.

L Steingisser et al: J Oncol Practice, 10 (5): e321-26, 2014

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1. Covered by BCBSMA policy – no notification required

↓

2. Covered by developed guidelines and clinical exceptions – notification required

↓

3. Covered based on clinical trial enrollment – documentation of trial required

↓

4. Covered based on peer to peer conversation – required if developed guidelines & exceptions are not met

↓

5. Covered based on appeal – required if not approved by peer to peer conversation (*PAC members instrumental in the adjudication of appeals)

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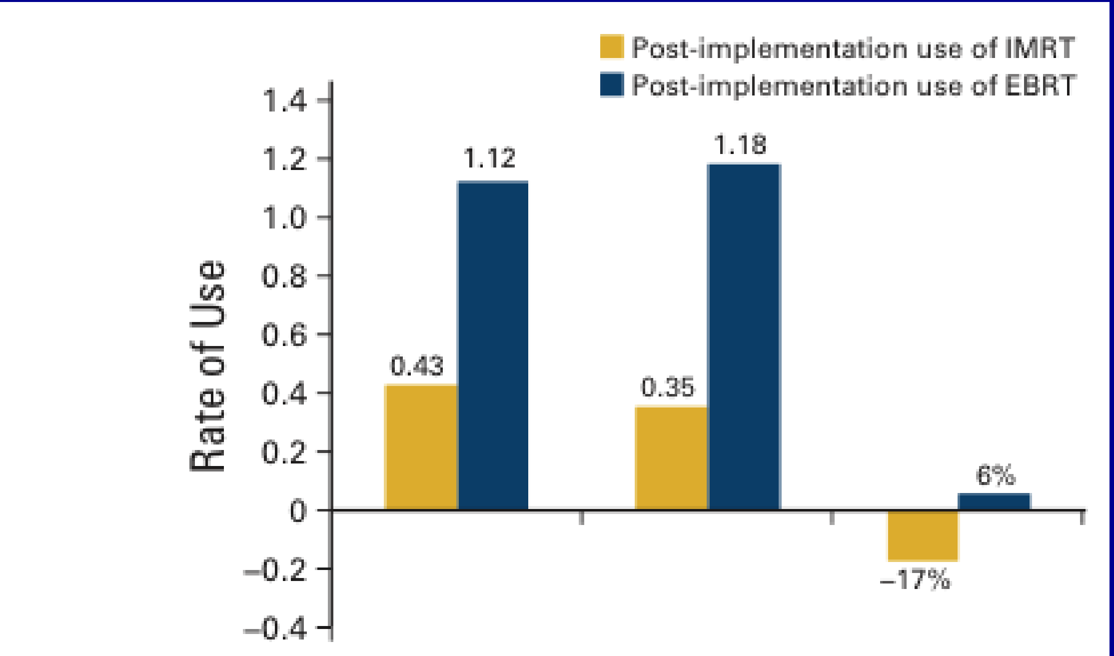

	Q4 2010 to Q3 2011	Q4 2011 to Q3 2012	% change
Post-implementation use of IMRT	0.43	0.35	-17%
Post-implementation use of EBRT	1.12	1.18	6%

- **During the two years prior to program implementation, IMRT use had increased by 20%, while conventional radiation had decreased by 3%**

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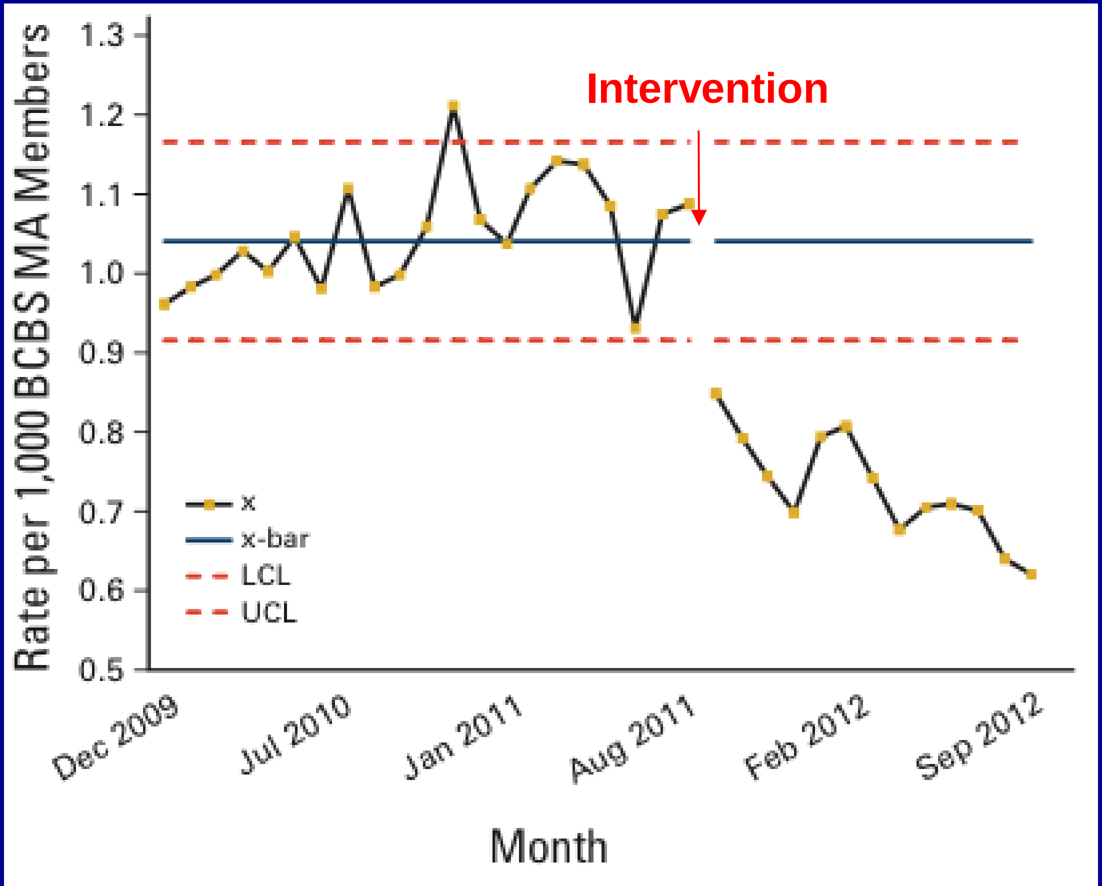
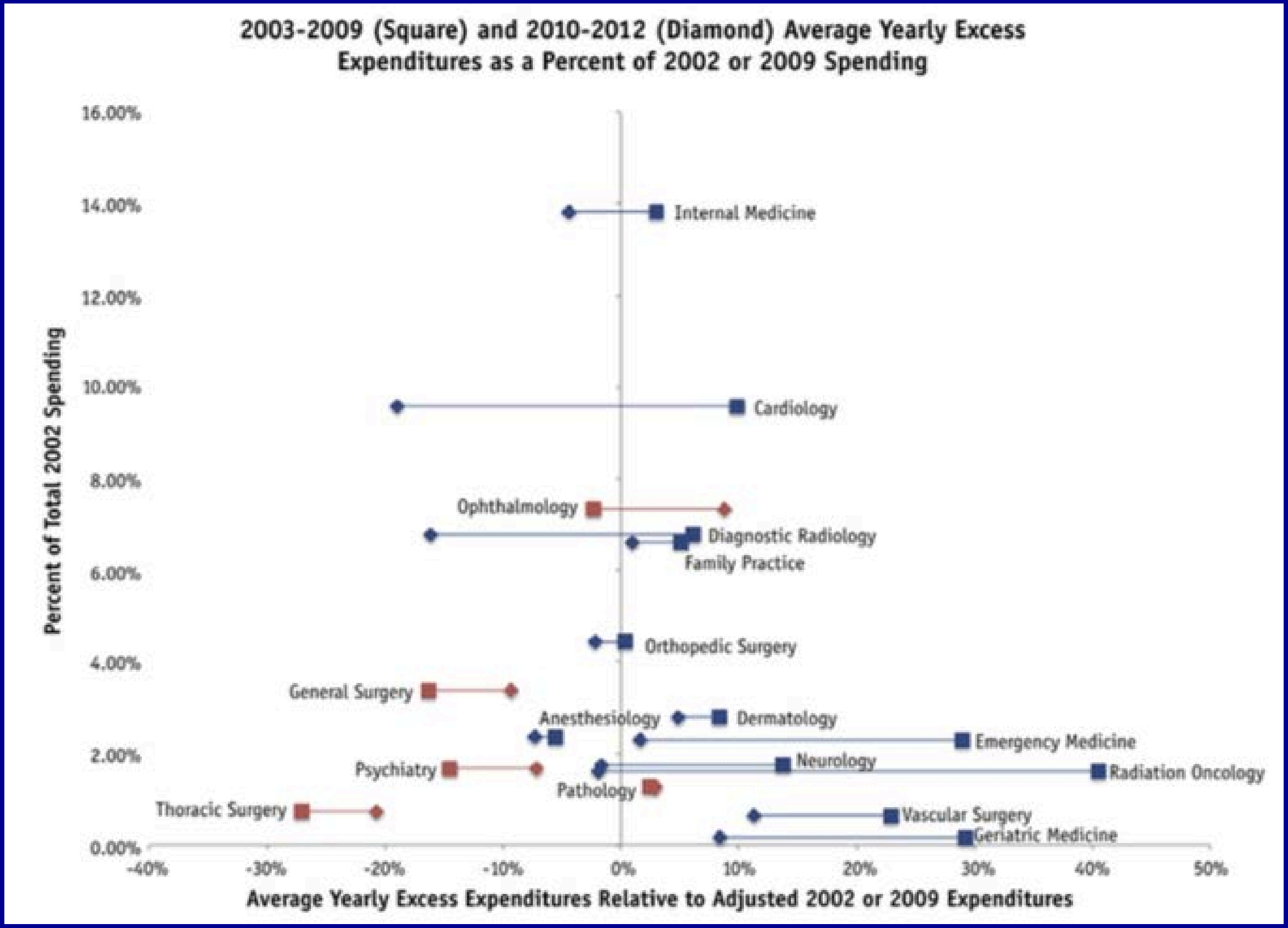


Following the intervention, each data point below the extended control limits confirms the presence of a new process.

L Steingisser et al: J Oncol Practice, 10 (5): e321-26, 2014

Revisiting the Sustainable Growth Rate "Hole": Sources of Healthcare Cost Stabilization 2010-2012



A Maroongroge et al: Int J Radiation Oncol Biol Phys, 90 (5): 983-85, 2014

Unique Collaboration: Radiation Oncologists' Physician Advisory Council (PAC) and BCBS MA to Optimize Use of Advanced Technology

- BCBSMA collaboration with PAC resulted in:
  - consensus development of IMRT criteria, often in the absence of level 1 evidence;
  - significant decrease in IMRT utilization;
  - significant decrease in medical expenses with flat administrative expenses, and
  - continued common platform for communication between providers and an insurance organization responsible for cost and quality of care

- Establishing a community standard of care in collaboration with providers may be a useful model for other new technologies where the science is not mature and the clinical outcomes data are evolving

- BCBSMA leadership & PAC continues to meet to update IMRT guidelines and to discuss utilization/guideline development of other advanced technologies (radiosurgery, protons)

L Steingisser et al: J Oncol Practice, 10 (5): e321-26, 2014

Closing Thoughts

• EBRT is a safe and effective treatment, dose escalation improves cancer control without increasing the risk of serious side-effects

• Technology is great but it can be seductive and expensive

• Proton therapy has some physical/dosimetric advantages over IMRT

• Protons can spare normal tissues and avoid the low dose radiation bath (decrease integral dose)

• Retrospective studies are mixed, some have shown potential decreased potential acute bowel and urinary morbidity compared to photons

• We must continue to invest in and promote scientific innovation and creativity while developing requisite evidence and looking to decrease cost

• Encourage collaborate proactive models of payer involvement