Future Directions in Prostate Cancer:
The Case for Protons

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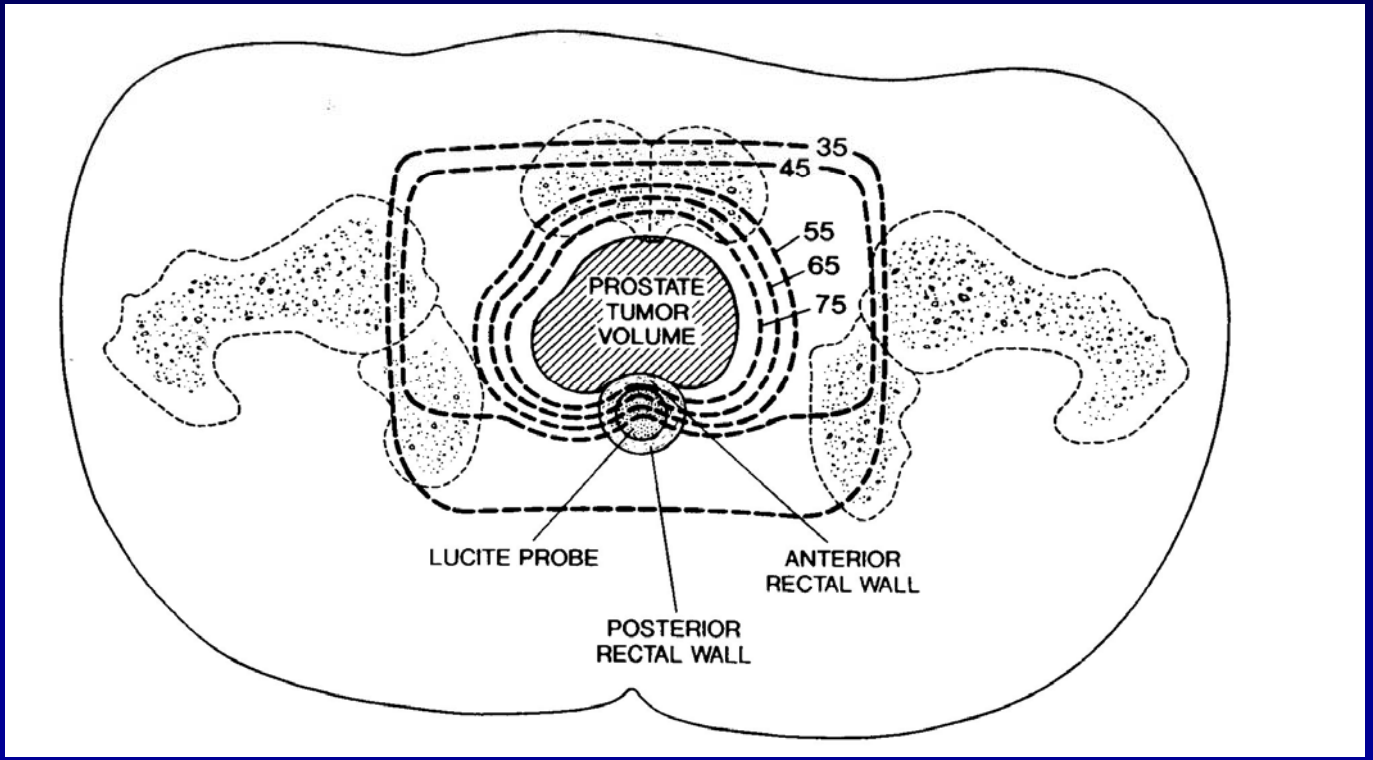
Protons and prostate cancer

- Early proton experience at the MGH
- The case for higher doses
  - PSA era randomized trials
- The means of higher doses
  - Brachytherapy
  - Conformal EBRT
    - Protons, photons and intensity modulation
- Future directions

The first use of proton radiation in prostate cancer

Four field photons plus a perineal proton boost (160 Mev)



Shipley, JAMA 241: 1912, 1979

Dose Escalation in Prostate Cancer
Supported by Randomized Data

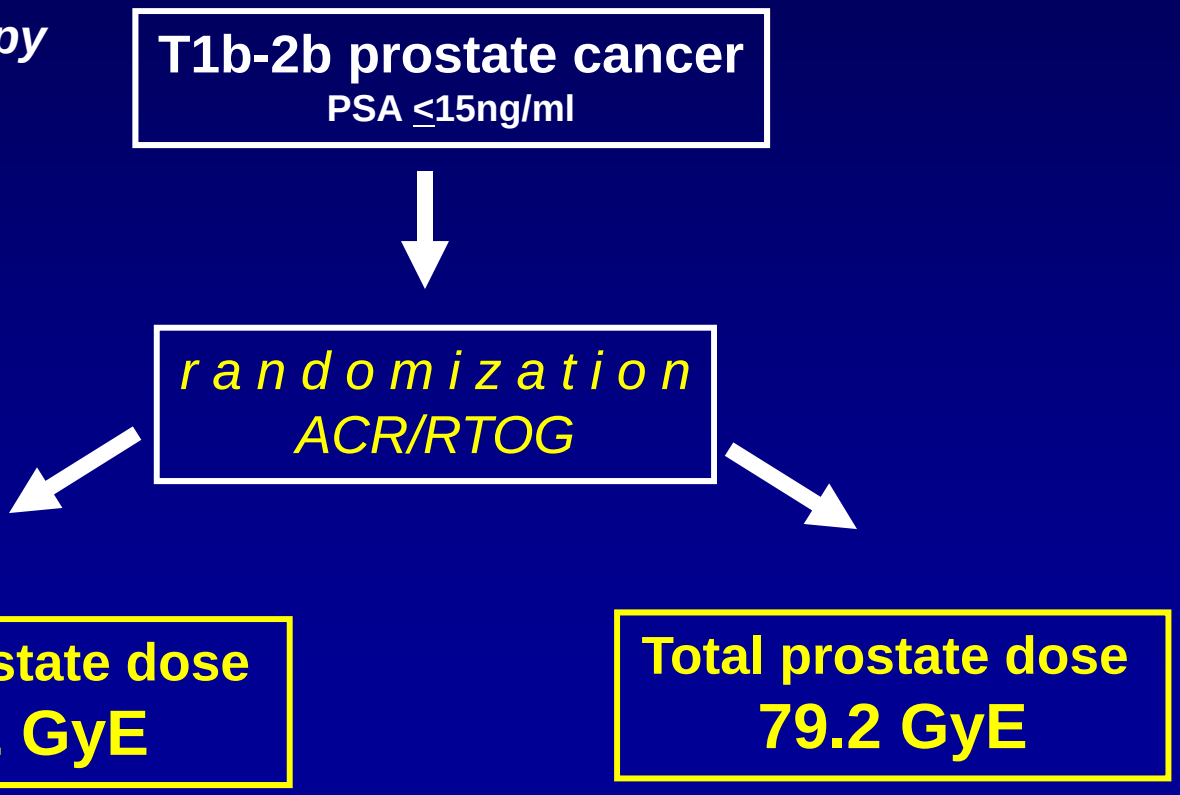
	doses	n	Low dose	High dose	P-value
MDACC	70 vs 78Gy	301	59%	78%	0.004
Dutch trial	68 vs 78Gy	669	54%	64%	0.02
UK MRC	64 vs 74Gy	843	60%	71%	0.0007
PROG 9509	70.2 vs 79.2GyE	393	79%	91%	<0.001

PROG 9509

Dose escalation using photons/protons

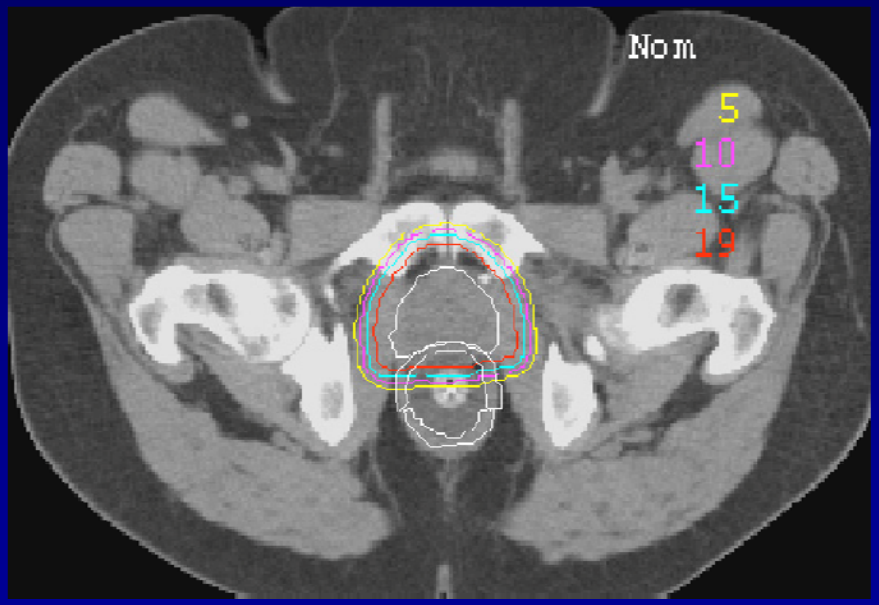
Trial design

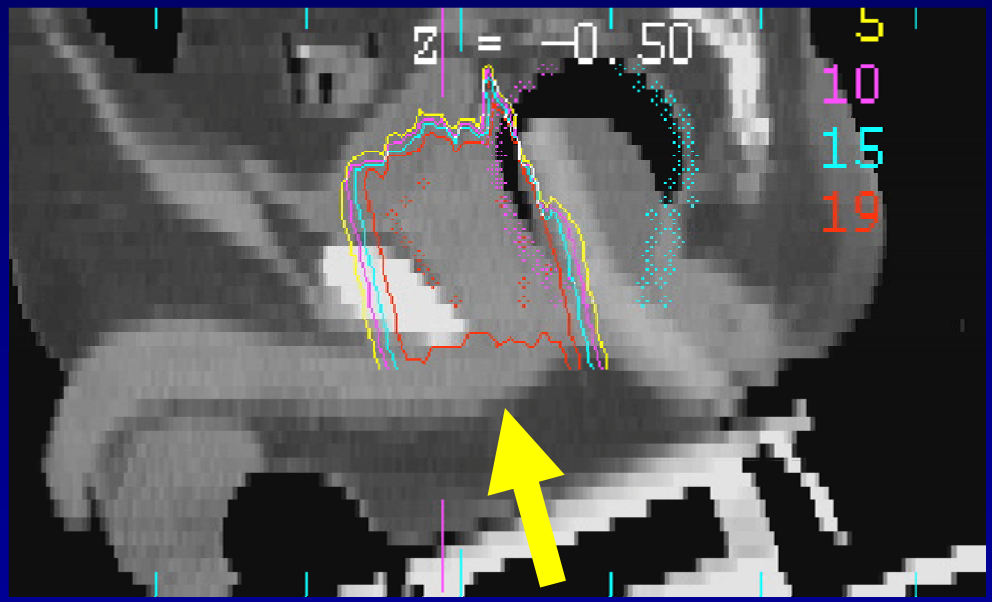
No hormonal therapy



PROG 9509

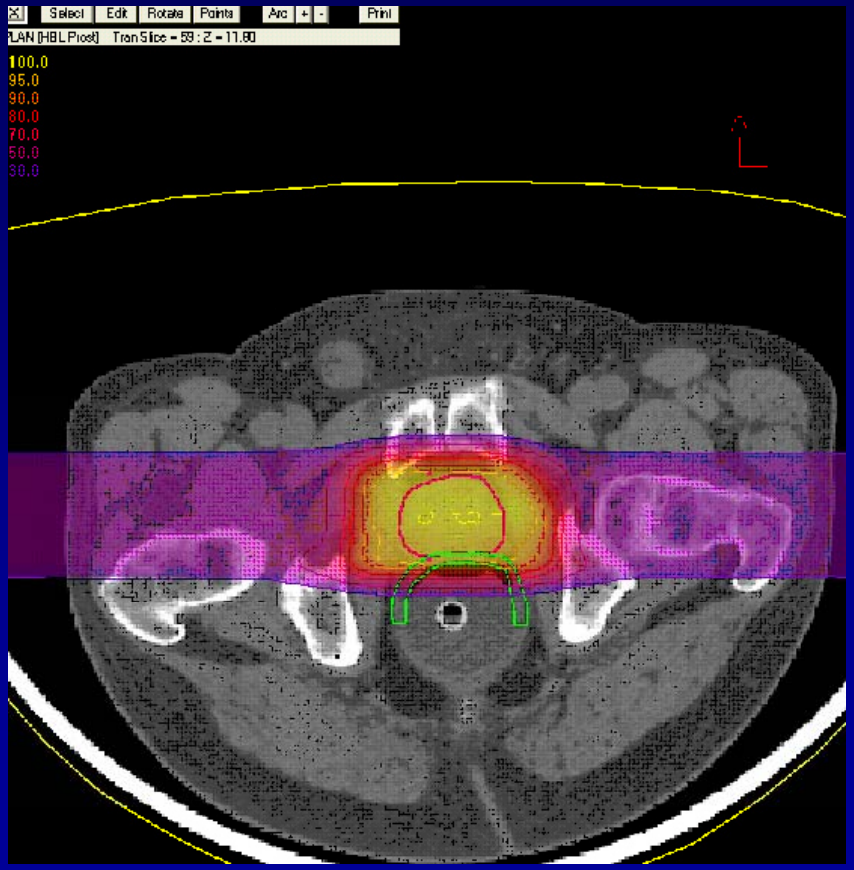
Prostate boost with protons - MGH

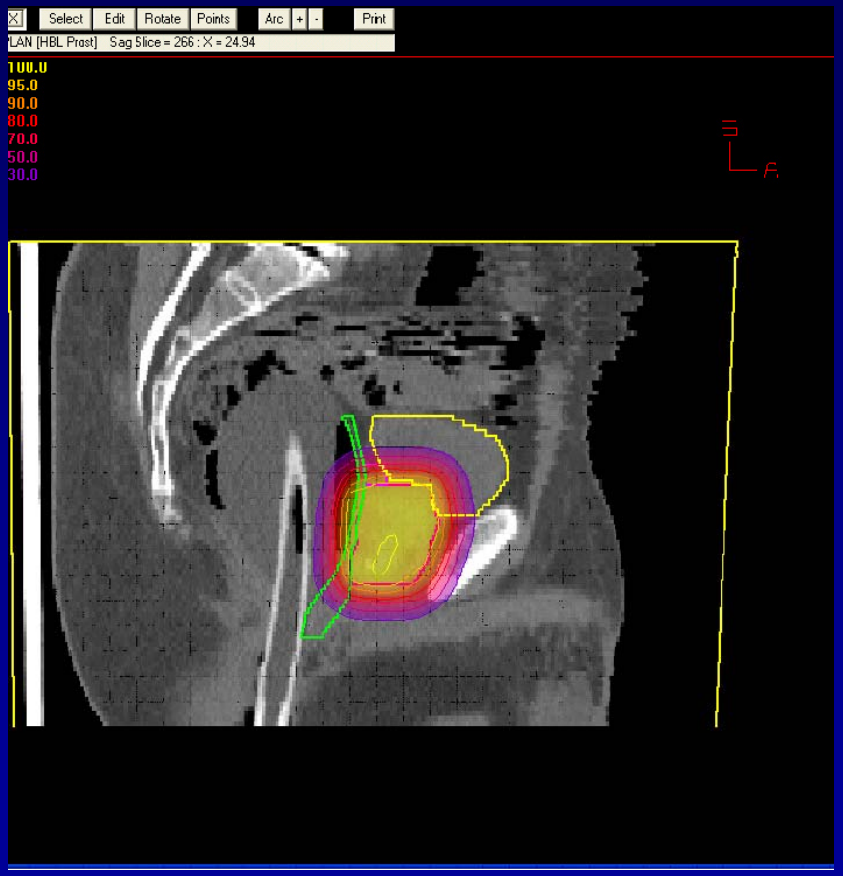




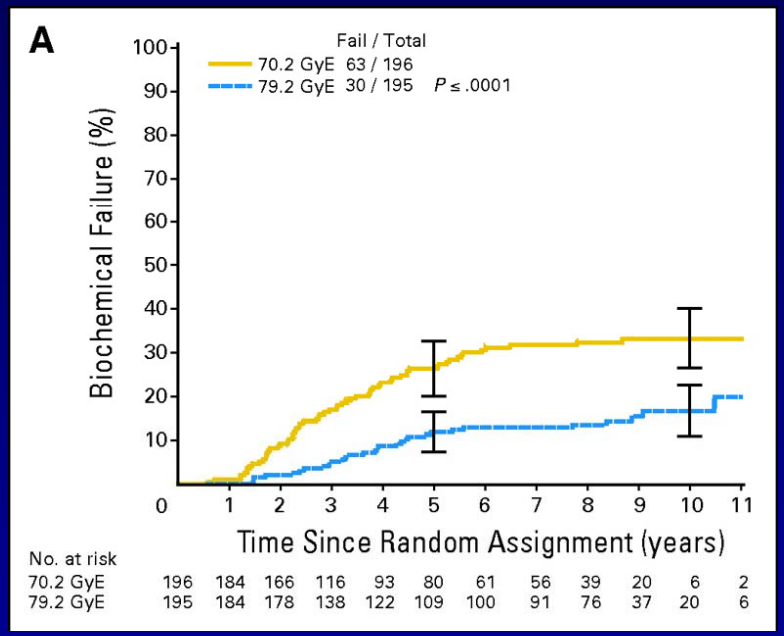
PROG 9509

Prostate boost with protons - LLUMC

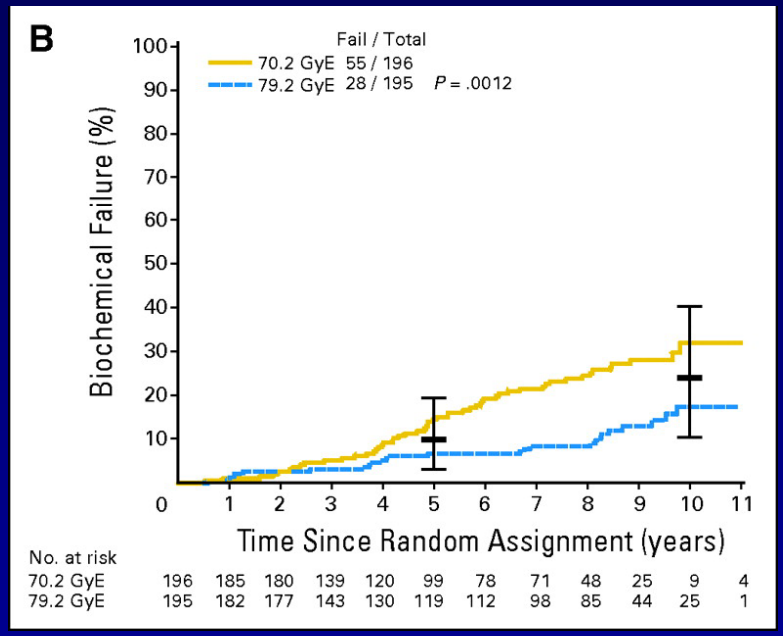




PROG 95-09



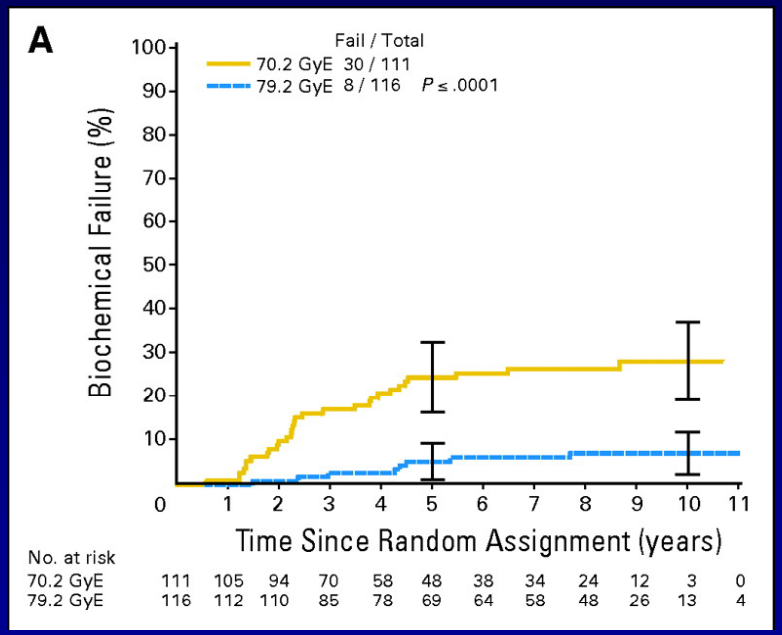
ASTRO



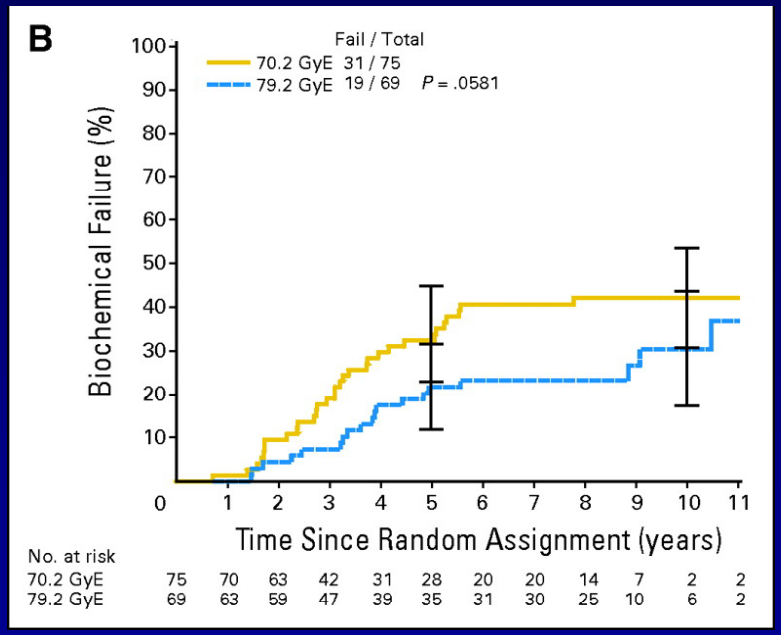
Phoenix

Zietman et al JCO 2010

PROG 95-09



Low risk

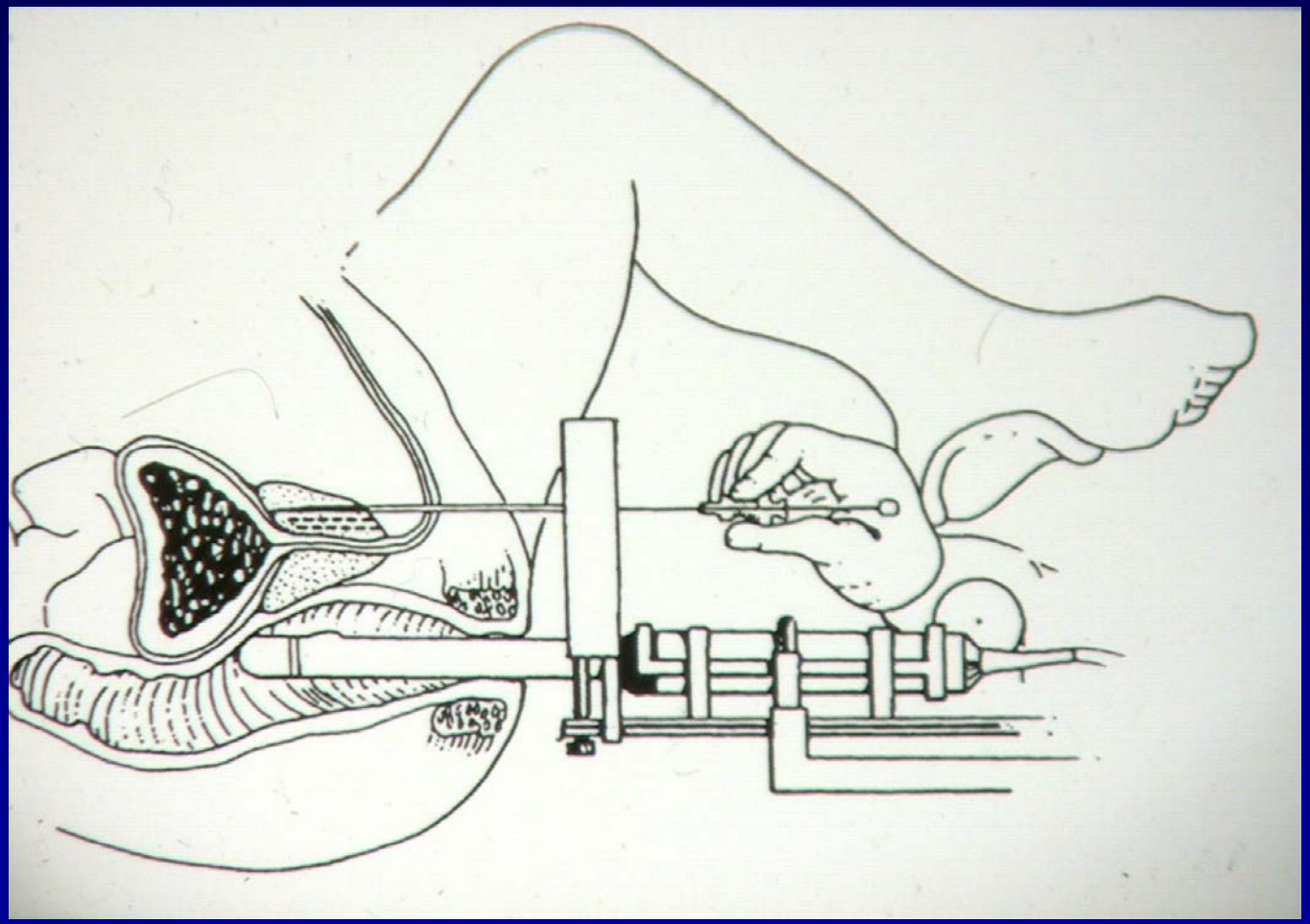


Intermediate risk

PSA era dose escalation studies

- Suggest benefits to higher doses
  - Improved bNED survival
  - High dose treatment is tolerable with either
    - 3D conformal treatment
    - IMRT
    - Protons

What about brachytherapy?



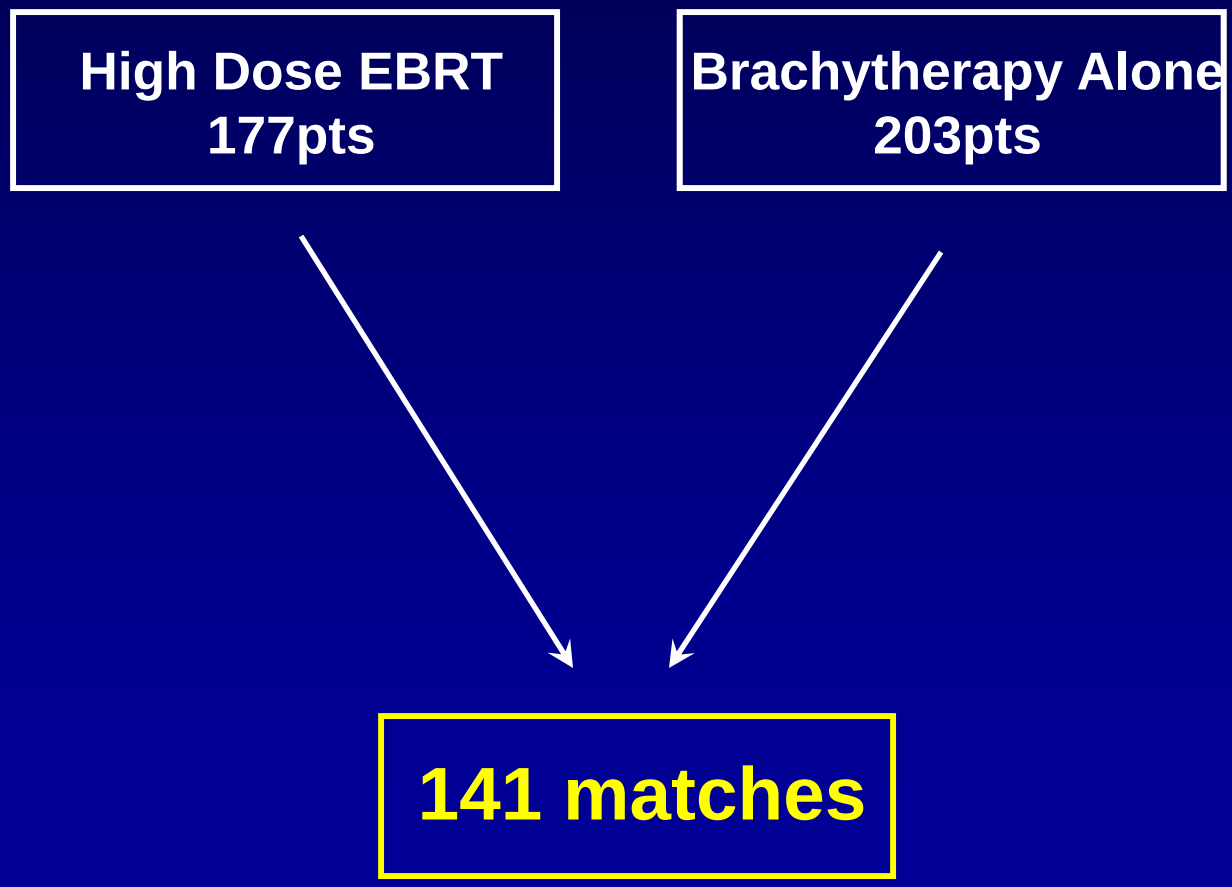
Case Matched Analysis

- High dose arm of PROG 9509
  - 79.2 CGE using a proton boost
  - 196 pts accrued from 1/31/96 to 12/31/99
  - 177 with GS ≤ 7 used for case matching
- Brachytherapy by a single brachytherapist (ALZ) from 1997-2000 at MGH
  - 203 similar pts treated with brachytherapy alone
    - 145 Gy I-125 or 115 Gy Pd-103

Coen et al IJROBP 2012

Case Matched Analysis

- Matched for
  - Tstage
  - Gleason score
  - PSA
  - Age



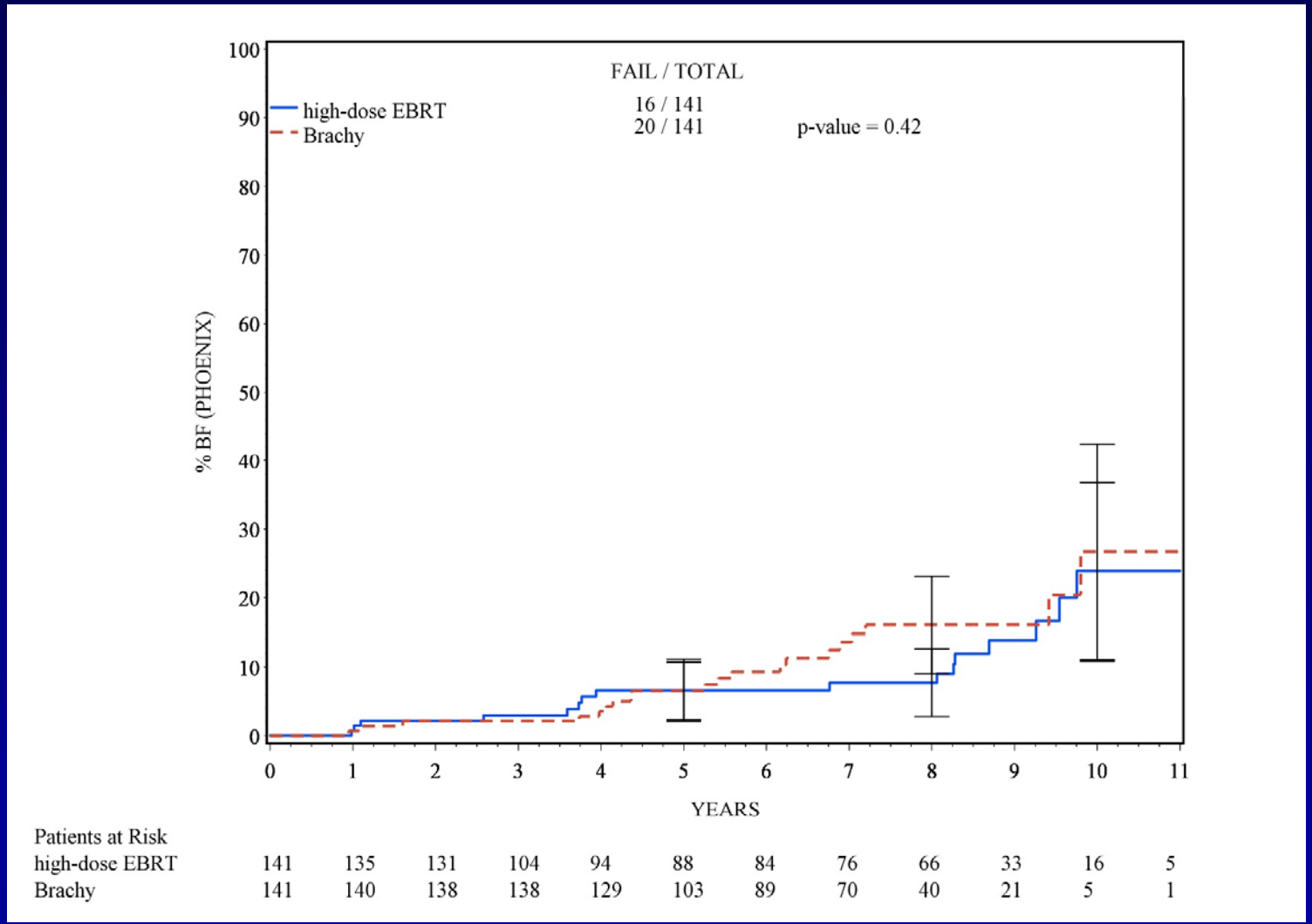
Case Matched Analysis
Patient Characteristics

	EBRT	Brachytherapy
Age (median)	67	65
PSA	6.1	5.6
Follow-up (yrs)	8.6	7.4

Patient Characteristics

	EBRT (n=141)	Brachytherapy (n=141)
Tstage		
1c	104 (74%)	104 (74%)
2a	36 (25%)	36 (25%)
2b	1 (1%)	1 (1%)
Gleason		
6	125 (89%)	125 (89%)
7	16 (11%)	16 (11%)
PSA		
<=4	17 (12%)	28 (20%)
4-10	112 (79%)	107 (76%)
10-15	12 (9%)	6 (4%)

Biochemical Failure

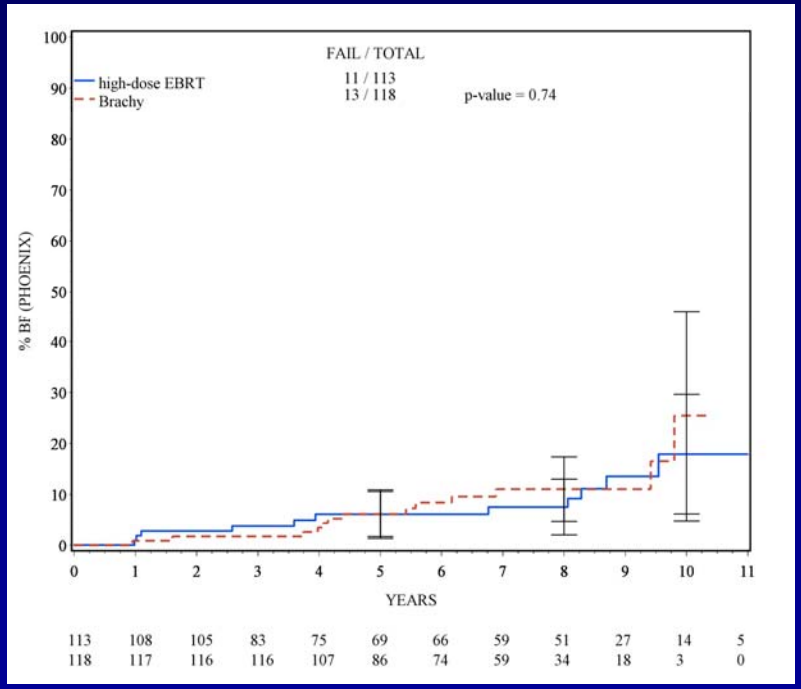


Risk Group Stratification

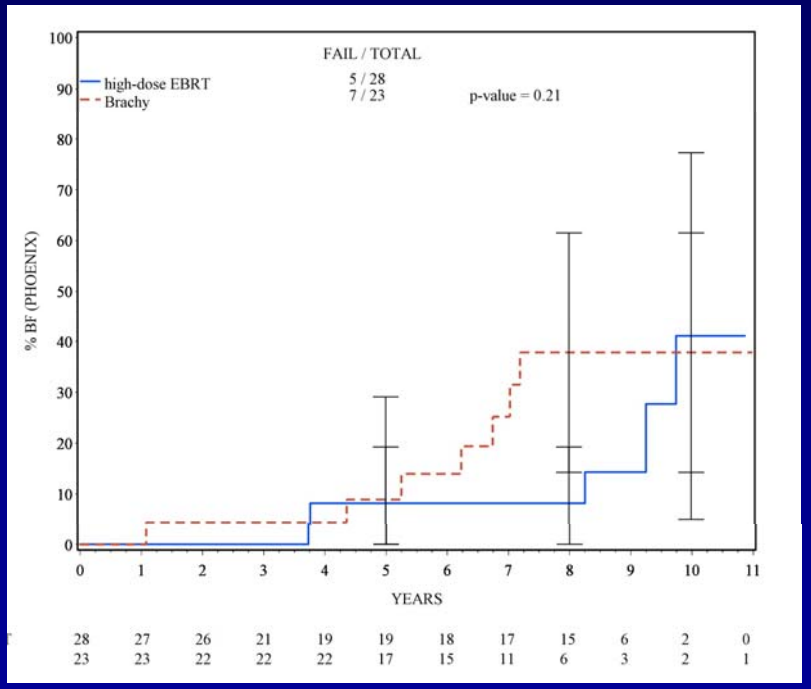
	EBRT (n=141)	Brachytherapy (n=141)
Risk group		
Low	113 (80%)	118 (84%)
Intermediate	28 (20%)	23 (16%)

BF by risk group

Low risk



Intermediate risk



BF Phoenix

8 yr BF	EBRT	Brachytherapy	P-value
Overall	7.7%	16.1%	P=0.42
Low risk	7.5%	11%	P=0.74
Intermediate risk	8.2%	38%	P=0.21

Nadir PSA

	EBRT	Brachytherapy
Nadir (median)*	0.3	0.1
Time to nadir (median)	60 mths	56 mths

*** Ttest p=0.001**

PSA at last follow-up
failure free patients

Last PSA	EBRT (n=129)	Brachytherapy (n=117)
≤0.5	85 (66%)	109 (93%)
0.5-1.0	24 (19%)	6 (5%)
>1.0	20 (15%)	2 (2%)

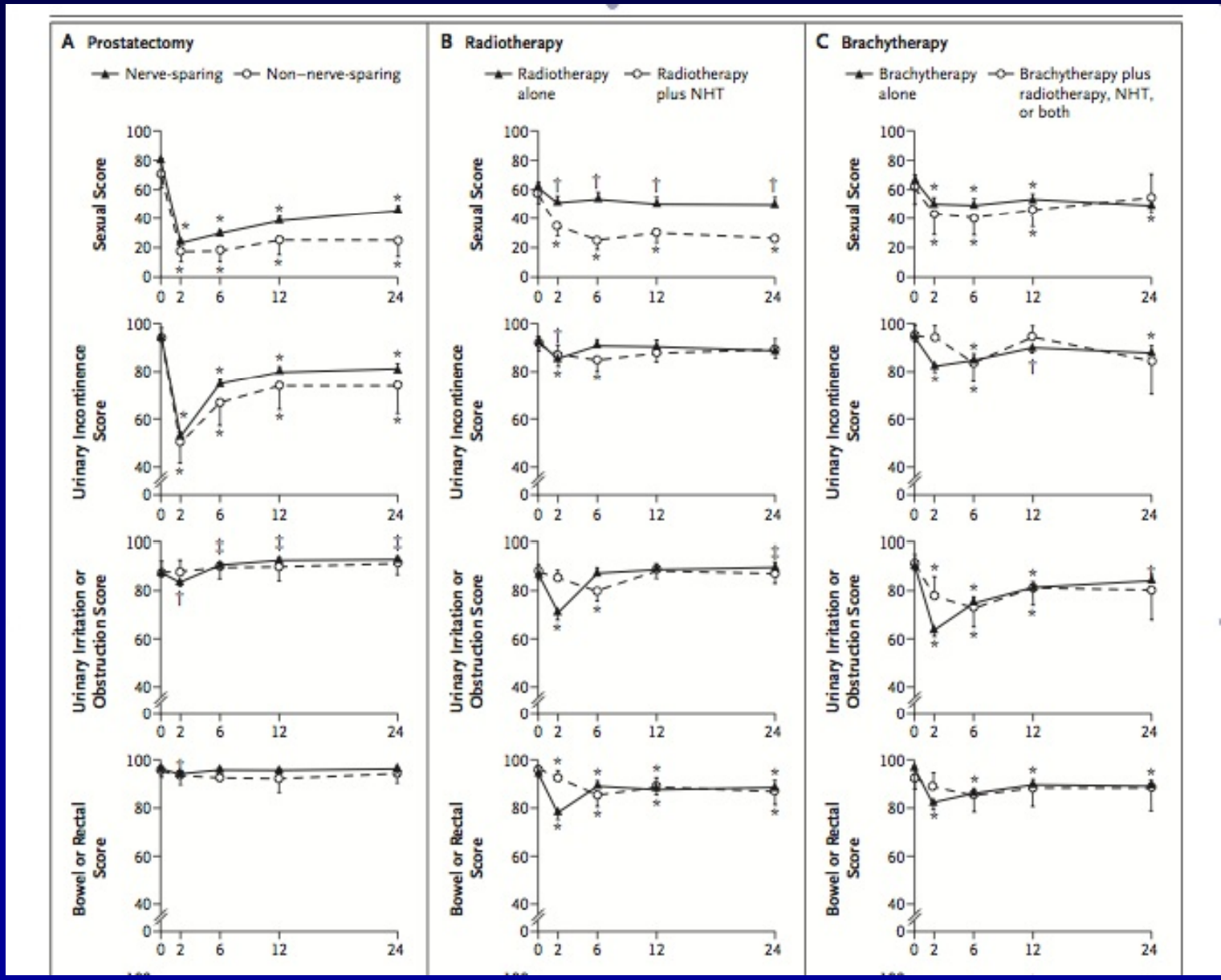
X-square p<0.0001

Case Matched Analysis
Conclusions

- High dose EBRT and brachytherapy appear equivalent in patients with low-intermediate risk prostate cancer
- Brachytherapy results in lower PSAs in patients free of disease
- QOL assessments may guide treatment decisions in the future

QOL assessment of current therapies

Longitudinal QOL comparisons using the EPIC instrument



Sanda et al NEJM 2008

PROG 95-09 QOL analysis

Scale	Prostate Cancer Symptom Indices Response Score: Standard Dose No. of Patients	Standard Dose Mean (SD)	High Dose No. of Patients	High Dose Mean (SD)	All No. of Patients	All Mean (SD)	*P* Value[b]
Urinary obstruction and irritation							
Urinary obstruction and irritation[c]	132	23.3 (13.7)	132	24.6 (14.0)	264	24.0 (13.9)	.36
Urinary obstruction and irritation, bother[d]	123	12.0 (16.5)	123	11.9 (15.1)	246	12.0 (15.8)	.80
Urinary incontinence							
Urinary incontinence[c]	131	10.6 (17.7)	134	9.7 (15.8)	265	10.2 (16.7)	.99
Urinary incontinence, bother[d]	133	10.3 (19.2)	134	8.4 (15.3)	267	9.4 (17.4)	.63
Urinary incontinence quality of life[e]	129	92.2 (16.4)	134	93.3 (13.6)	263	92.7 (15.0)	.72
Bowel problems							
Bowel problems[c]	134	7.7 (7.8)	137	7.9 (9.1)	271	7.8 (8.4)	.70
Bowel problems, bother[d]	131	5.5 (10.2)	131	7.9 (12.4)	262	6.7 (11.4)	.10
Sexual function							
Sexual dysfunction[c]	132	68.2 (34.6)	127	65.9 (34.7)	259	67.1 (34.6)	.65
Sexual problems, bother[d]	124	44.5 (24.1)	122	45.1 (22.2)	246	44.8 (23.1)	.95
Sexual intimacy[f]	128	67.7 (28.8)	123	70.7 (27.4)	251	69.2 (28.1)	.44
Sexual confidence[f]	129	38.0 (30.7)	123	42.2 (31.3)	252	40.1 (31.0)	.30
Masculine self-esteem[f]	130	78.4 (23.5)	123	80.1 (20.8)	253	79.2 (22.2)	.92
Marital affect[f]	93	91.7 (17.7)	99	91.8 (17.0)	192	91.8 (17.3)	.83

Single survey – median 9.4 yrs post-tx

No diff in any QOL outcome

Talcott et al JAMA 2010

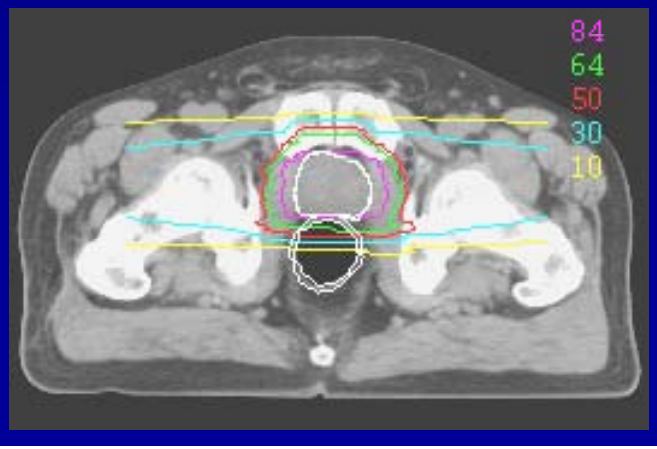
Further dose escalation using conformal protons

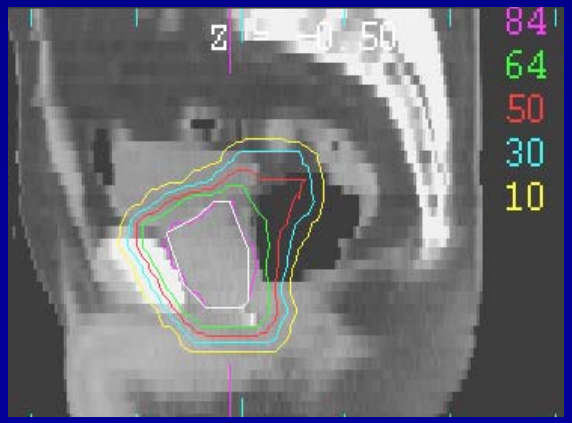
Phase I/II study - ACR 0312

Study of:

- **85 pts - Low/intermediate risk prostate cancer**
- **Further dose increase**
- **More convenient fractionation**
- **Protons alone**
- **Image guidance**

82GyE with 2GyE fraction





ACR 03-12 Late Toxicity

	Grade			
	1	2	3	4
Toxicity/category				
Urinary incontinence	1	0	0	0
Urinary frequency/urgency	36	12	5	0
Bladder/other GU	9	6	2	0
Skin	7	0	0	0
Small/large intestine	16	8	1	0
Other GI	8	1	0	1
Other	8	1	0	1
Worst non-GI/GU	8 (10%)	1 (1%)	0 (0%)	1 (0%)
Worst GI/GU	28 (33%)	22 (26%)	6 (7%)	1 (1%)
Worst overall	28 (33%)	22 (26%)	6 (7%)	1 (1%)

Abbreviations: GU = genitourinary; GI = gastrointestinal.

Coen et al IJROBP 2011

Long-term QOL analysis of men receiving 78-82GyE proton RT

	N	Baseline*	Long-term*	Change*	p-value**
Incontinence	71	3.2 (8.2)	10 (15)	6.6 (16)	<0.001
Obstruction/irritation	73	20 (9.8)	23 (12)	3.1 (11)	0.04
Bowel problems	72	4.3 (6.8)	8.2 (9.5)	3.5 (8.8)	<0.001
Sexual dysfunction	69	25 (34)	49 (34)	22 (31)	<0.001

* mean (standard deviation)
** Wilcoxon signed rank

Long term questionnaires ranged from 36-60 mths post-tx

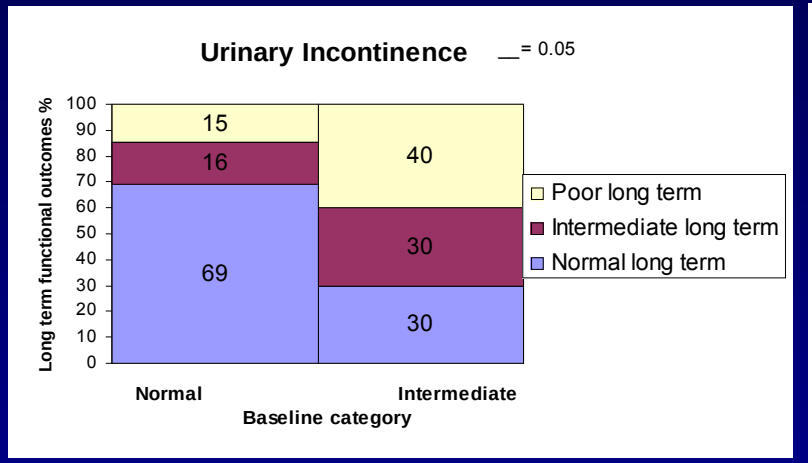
Coen et al IJROBP 2012

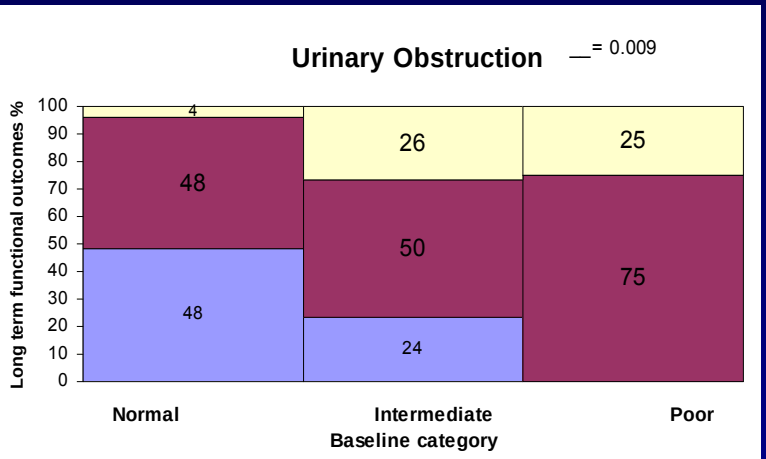
Long-term QOL analysis by baseline function

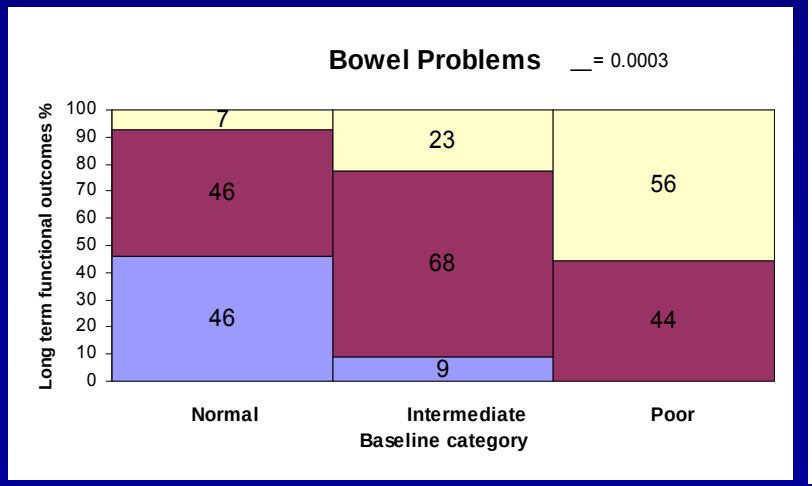
	N	Baseline*	Long-term*	Change*	p-value**
Incontinence					
Normal	61	0 (0)	8.3 (15)	8.3 (15)	<0.001
Intermediate	10	23 (6.4)	19 (15)	-3.5 (17)	0.5
Poor	0	N/A	N/A	N/A	N/A
total	71				
Obstruction/irritation					
Normal	27	11 (5.9)	17 (12)	5.8 (9.7)	0.004
Intermediate	34	24 (5.4)	27 (12)	3.2 (12)	0.2
Poor	12	32 (7.9)	28 (5.9)	-3.4 (11)	0.3
total	73				
Bowel problems					
Normal	41	0 (0)	5.2 (6.9)	5.2 (6.9)	<0.001
Intermediate	22	6.8 (3.3)	10 (11)	3.2 (10)	0.2
Poor	9	18 (7.5)	15 (9.6)	-3.2 (11)	0.5
total	72				
Sexual dysfunction					
Normal	29	1.4 (3.0)	30 (31)	28 (31)	<0.001
Intermediate	22	17 (9.9)	46 (28)	29 (24)	<0.001
Poor	18	76 (25)	78 (24)	2.6 (30)	0.5
total	69				

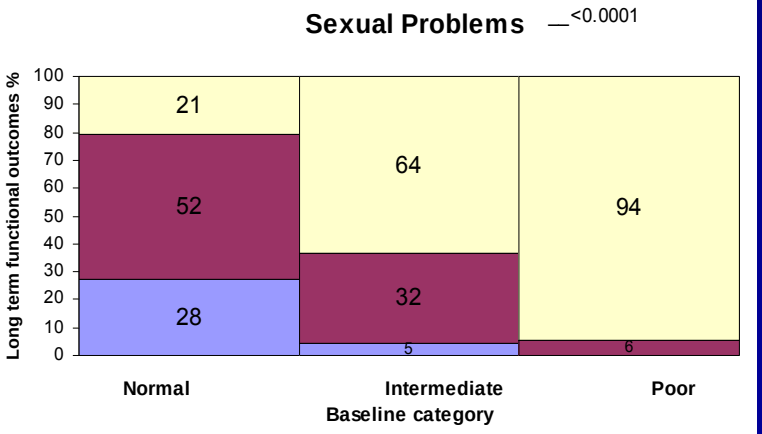
* mean (standard deviation)
**Wilcoxon signed rank

Long-term QOL analysis by baseline function





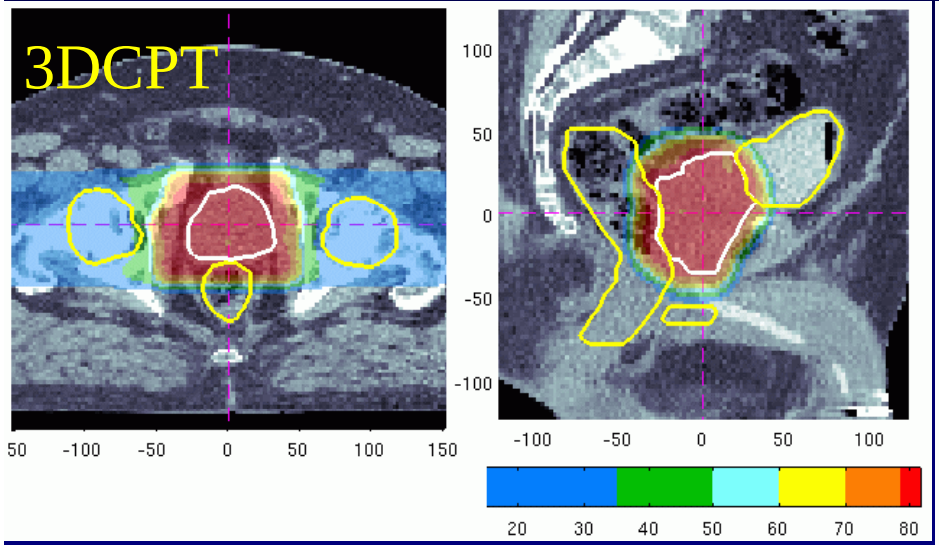


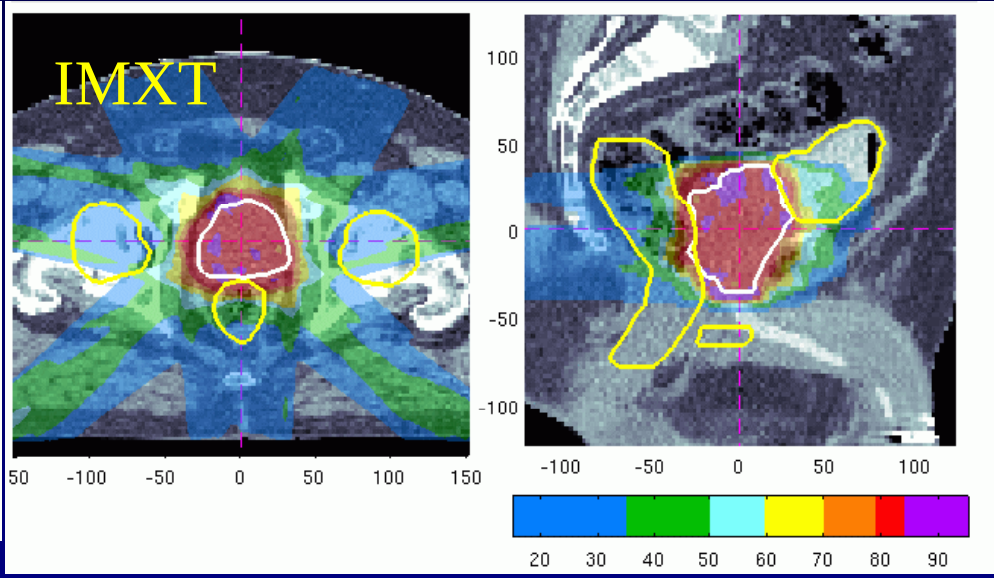


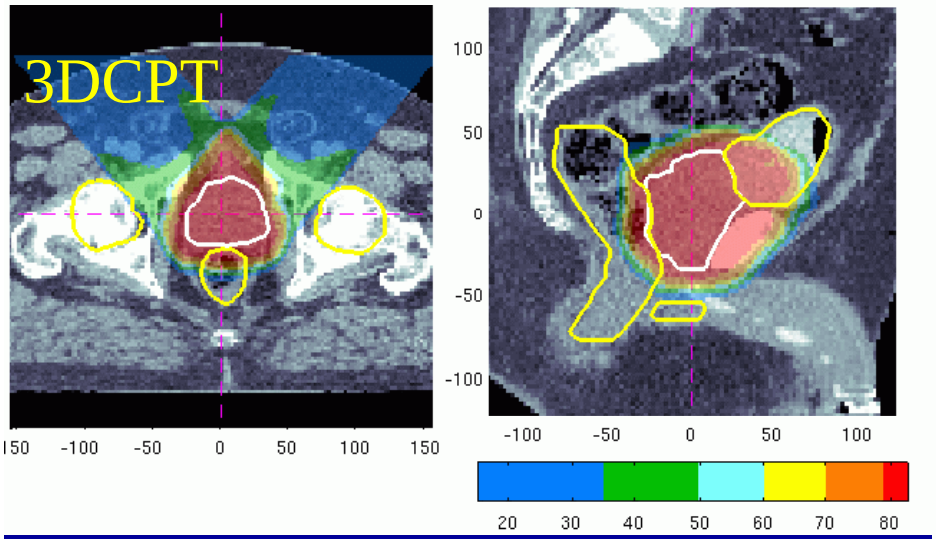
Refining high dose EBRT
The role of protons

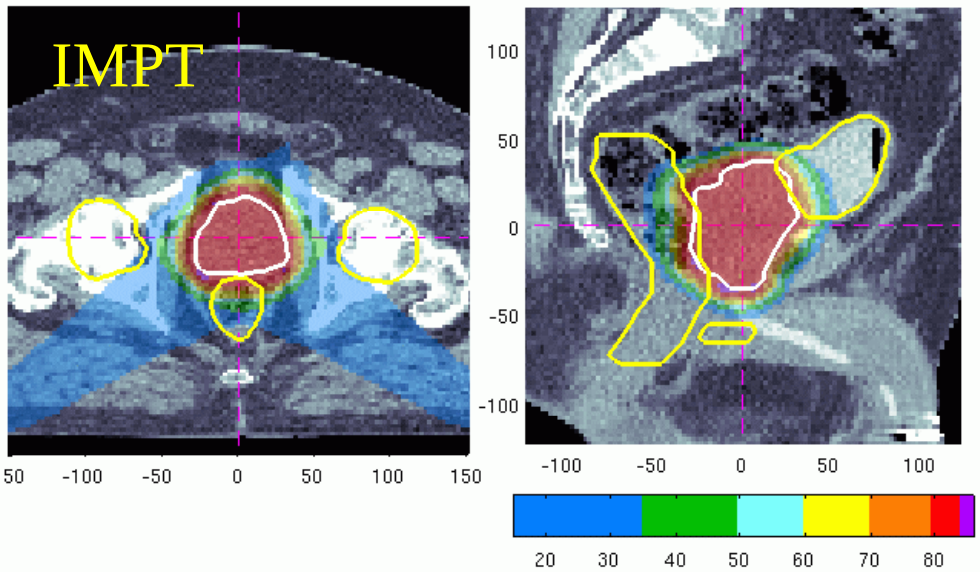
- Dose distribution comparisons
- Clinical trials
  - Quality of life endpoints
- Theoretical risks
  - Secondary malignancies
    - Integral dose
    - Neutron scatter

Dosimetric comparisons of protons vs IMRT

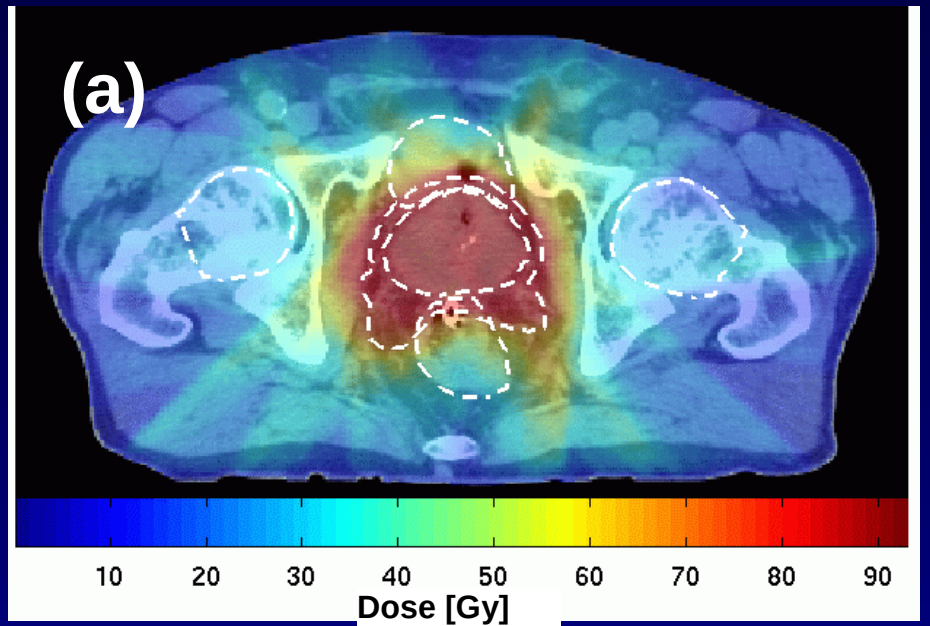


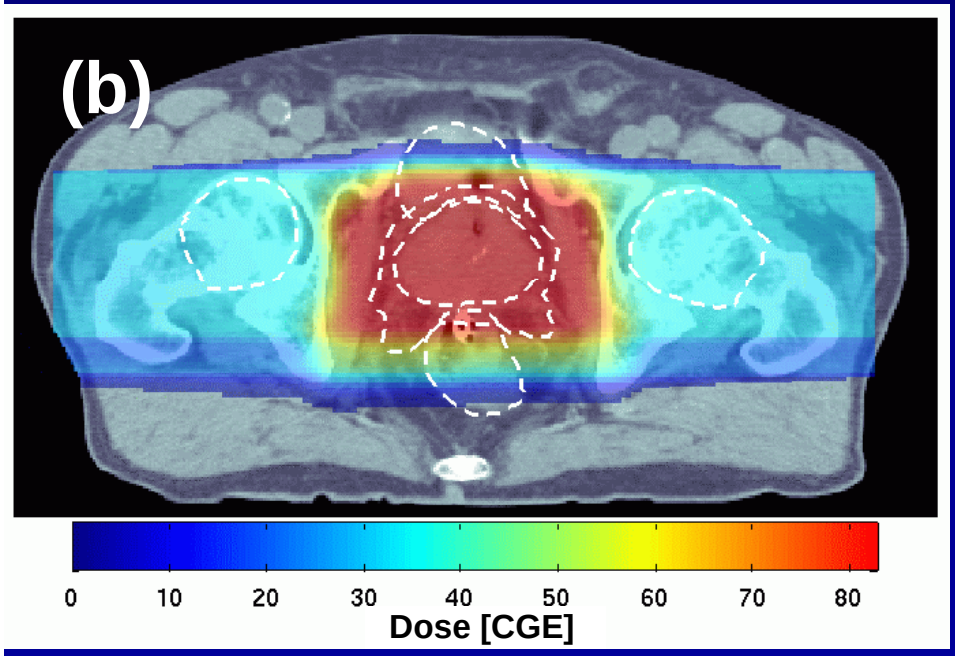


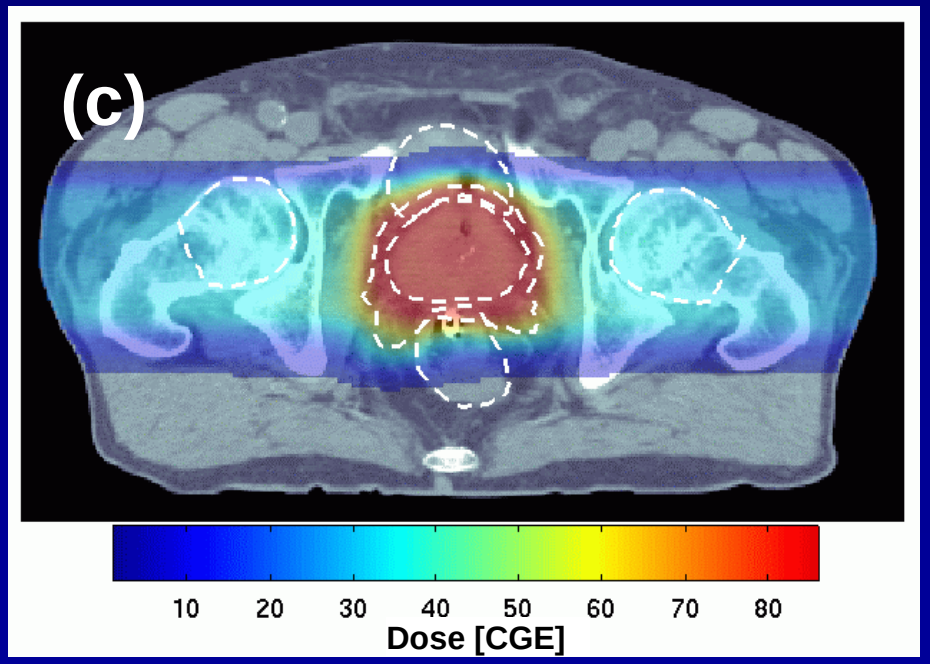




- **Dose distribution**
  - (a) IMRT
  - (b) 3d-conformal proton
  - (c) IMPT

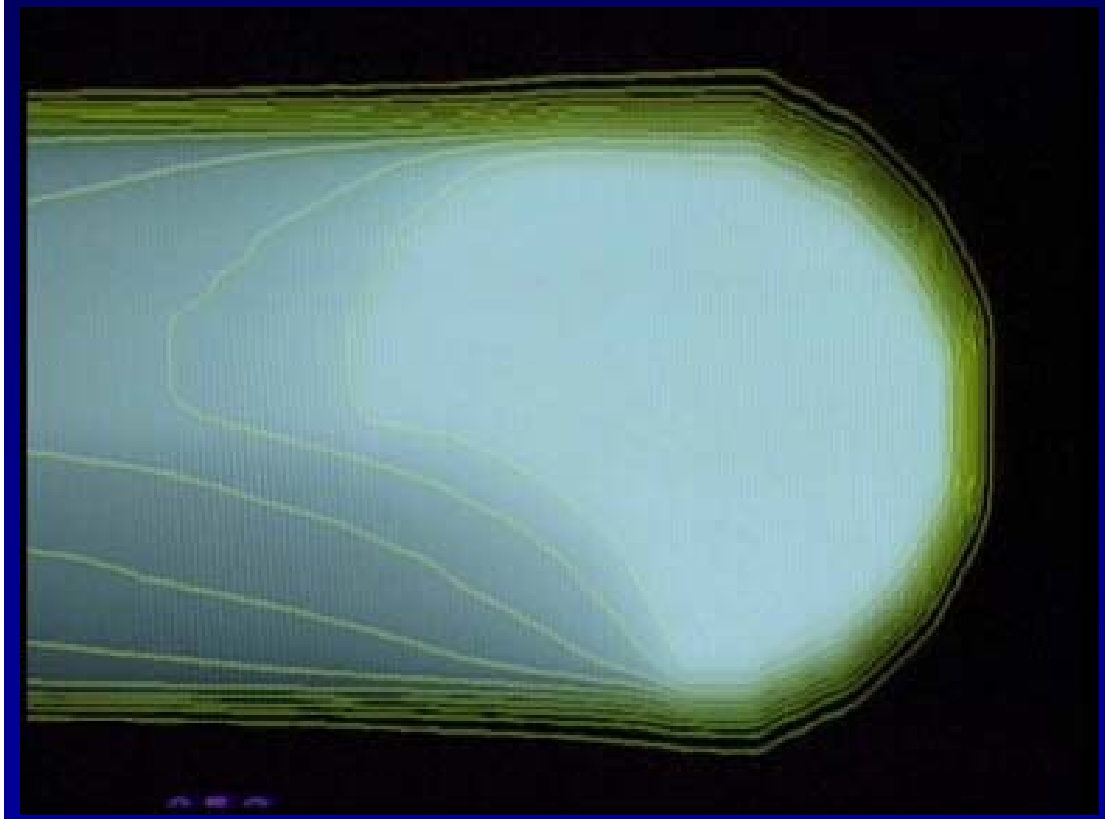






Intensity Modulated Proton Therapy (IMPT)
Spot Scanning - Principle

The dynamic application of scanned and modulated proton pencil beams

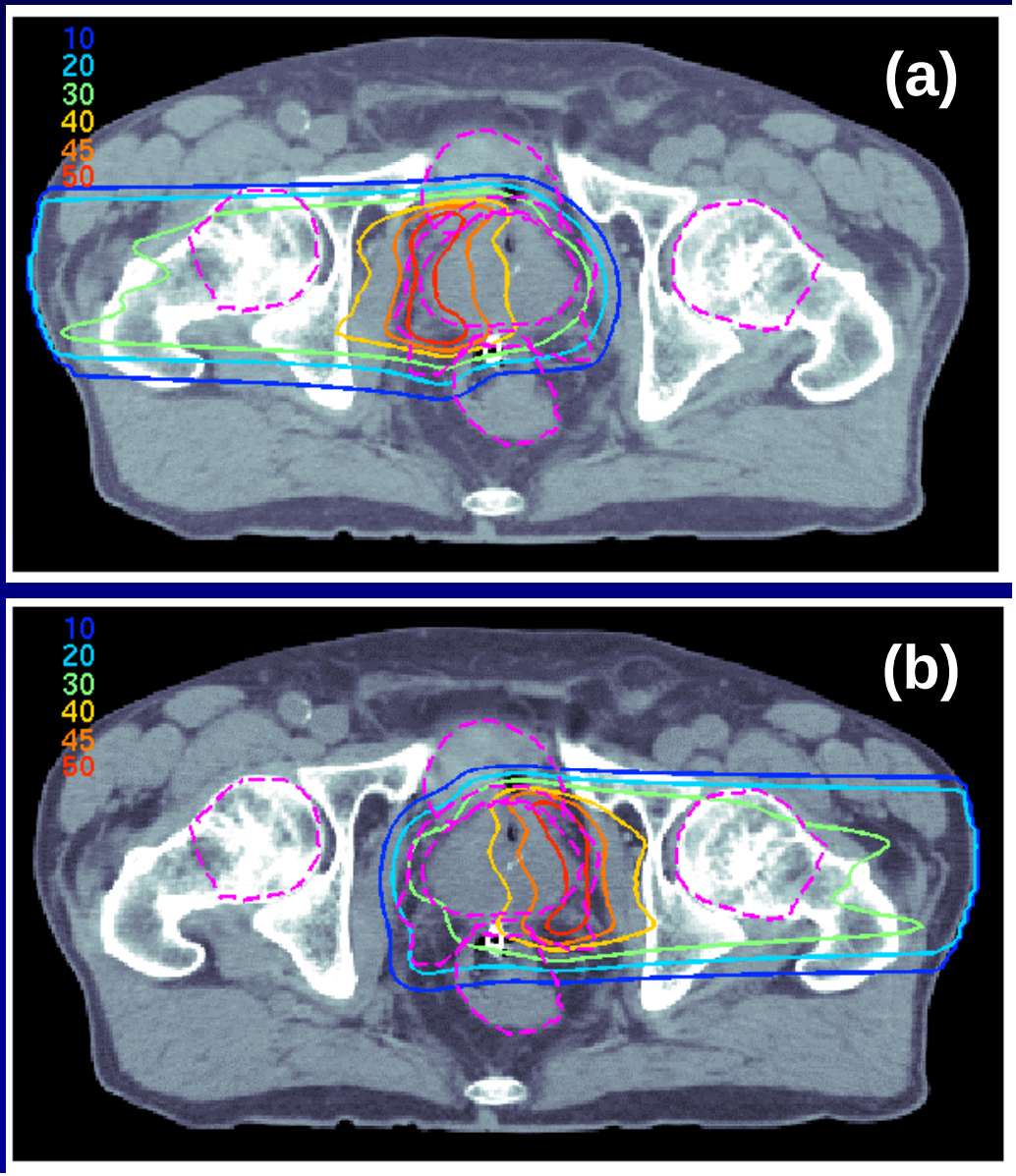


A full set, with a homogenous dose conformed distally *and* proximally

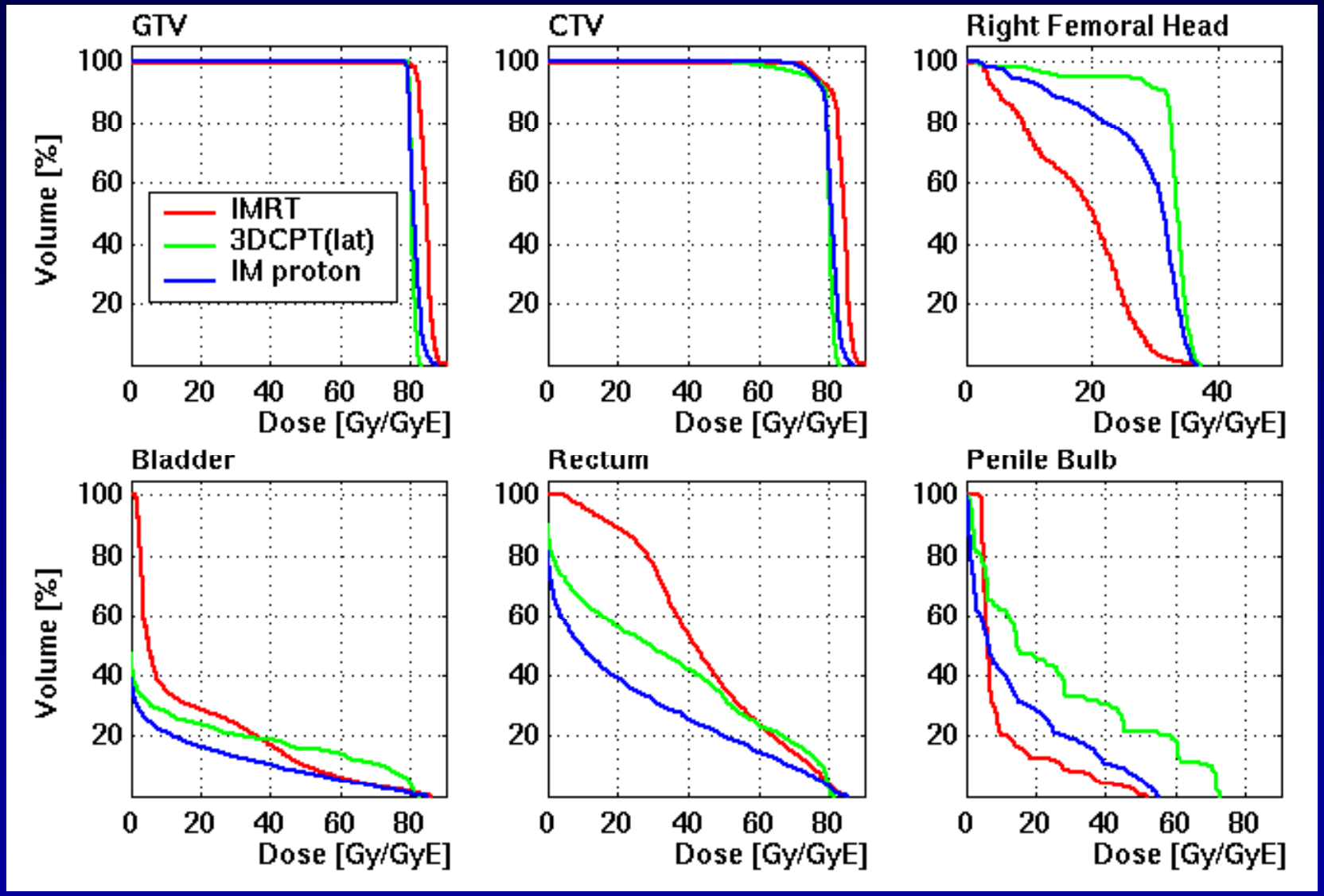
Images courtesy of Eros Pedroni

Intensity-modulated proton therapy

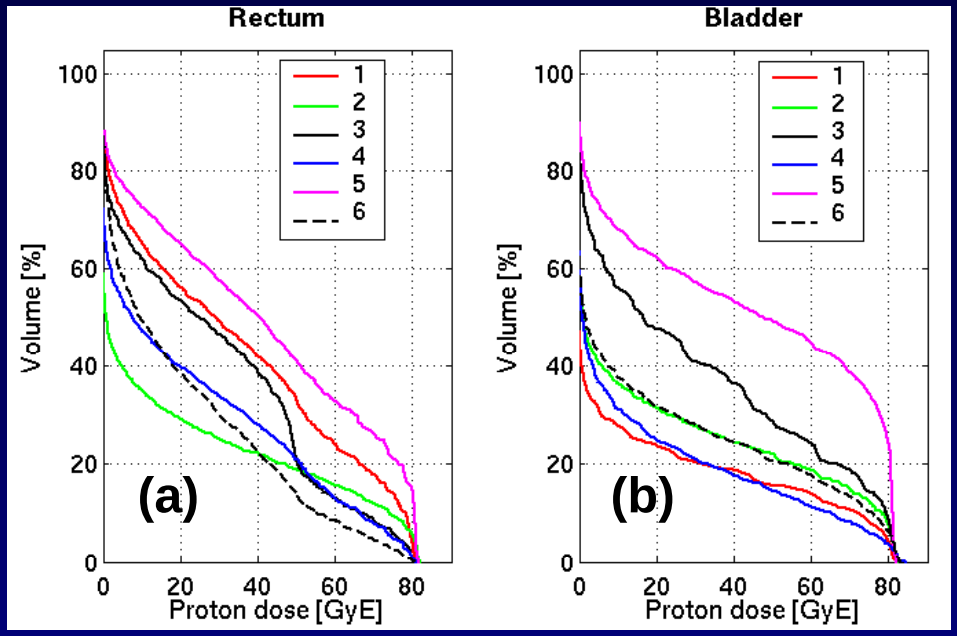
Lateral beams deliver inhomogeneous dose distributions, which combine to a homogeneous dose in the target volume

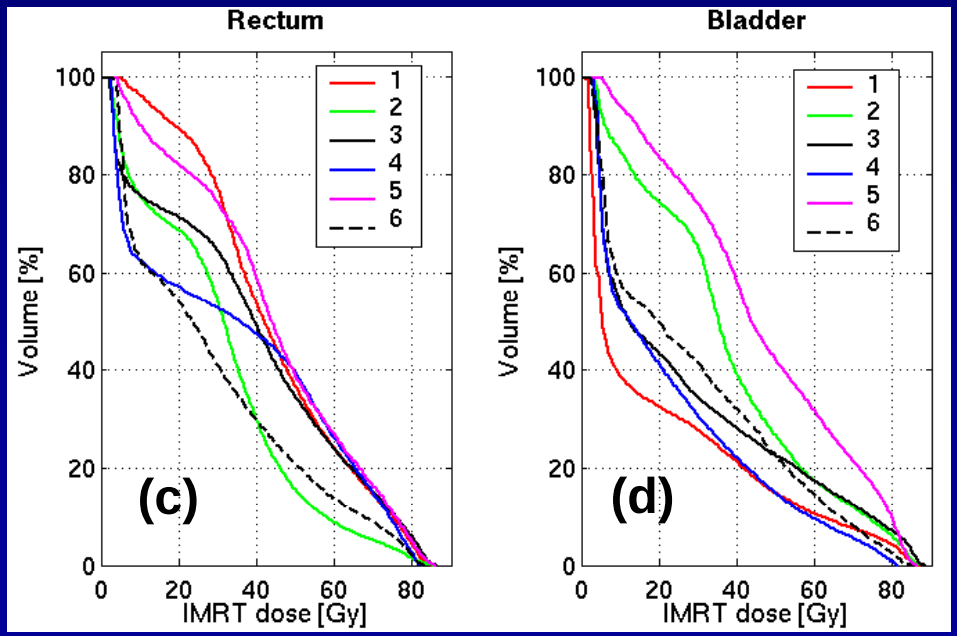


Dose volume histograms, from photon IMRT, 3D-CPT (parallel-opposed lateral beam configuration) and IMPT plans



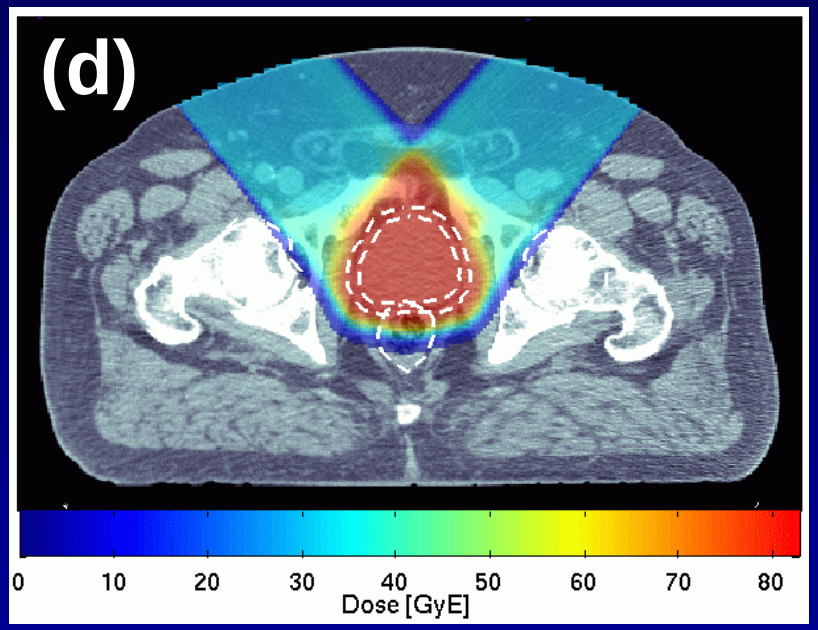
- **DVH data from 6pts**
  - **With 3D protons**
  - **IMRT**



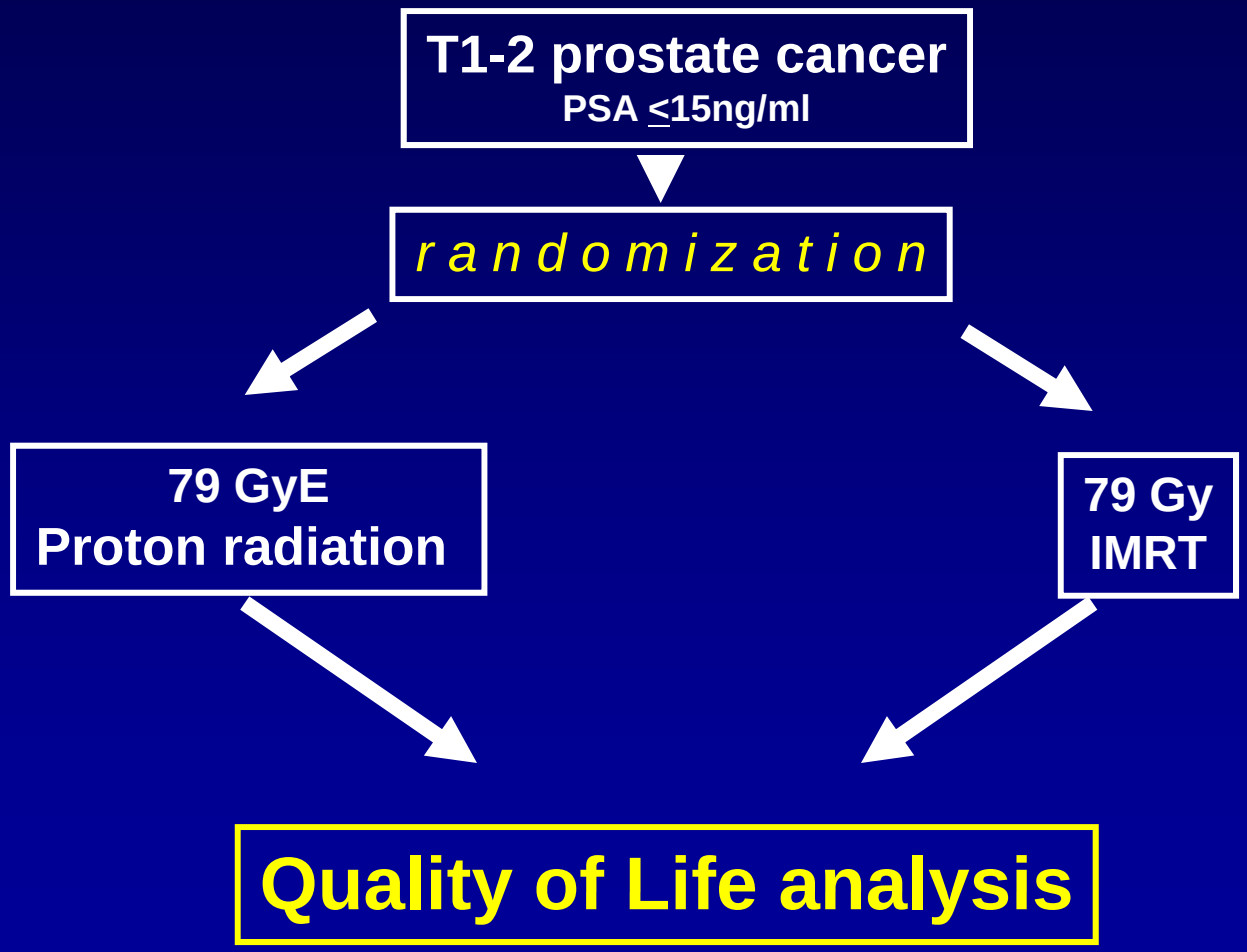


Technical issues with protons

- Limitations
  - Penumbra at depth
  - End of range uncertainty
  - Smearing
- Future directions
  - Non-traditional beam arrangements
  - Focal tumor boosting
- Image guidance is critical
  - Daily Target localization
  - Dosimetric recalculation

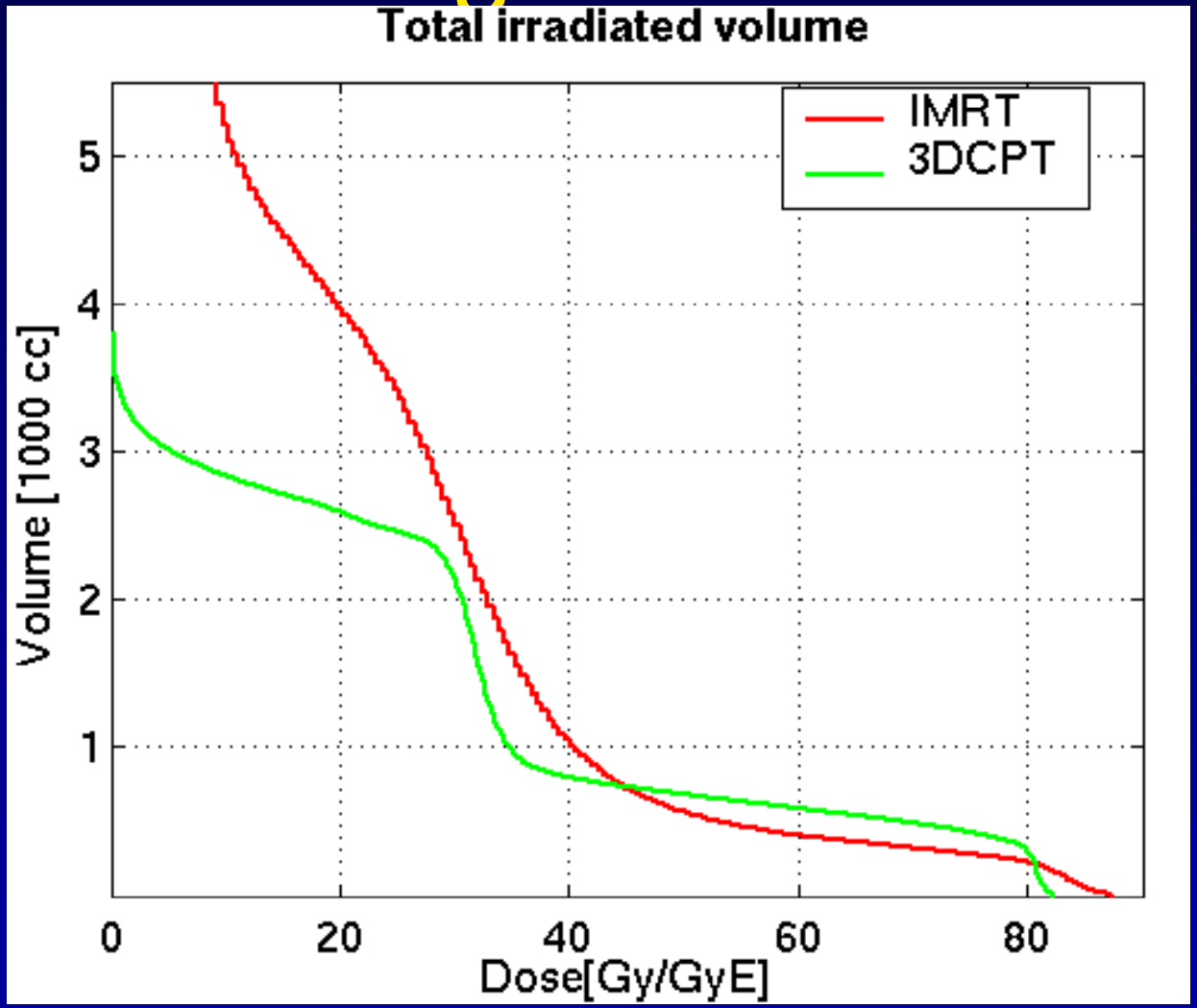


Now Open – QOL endpoint

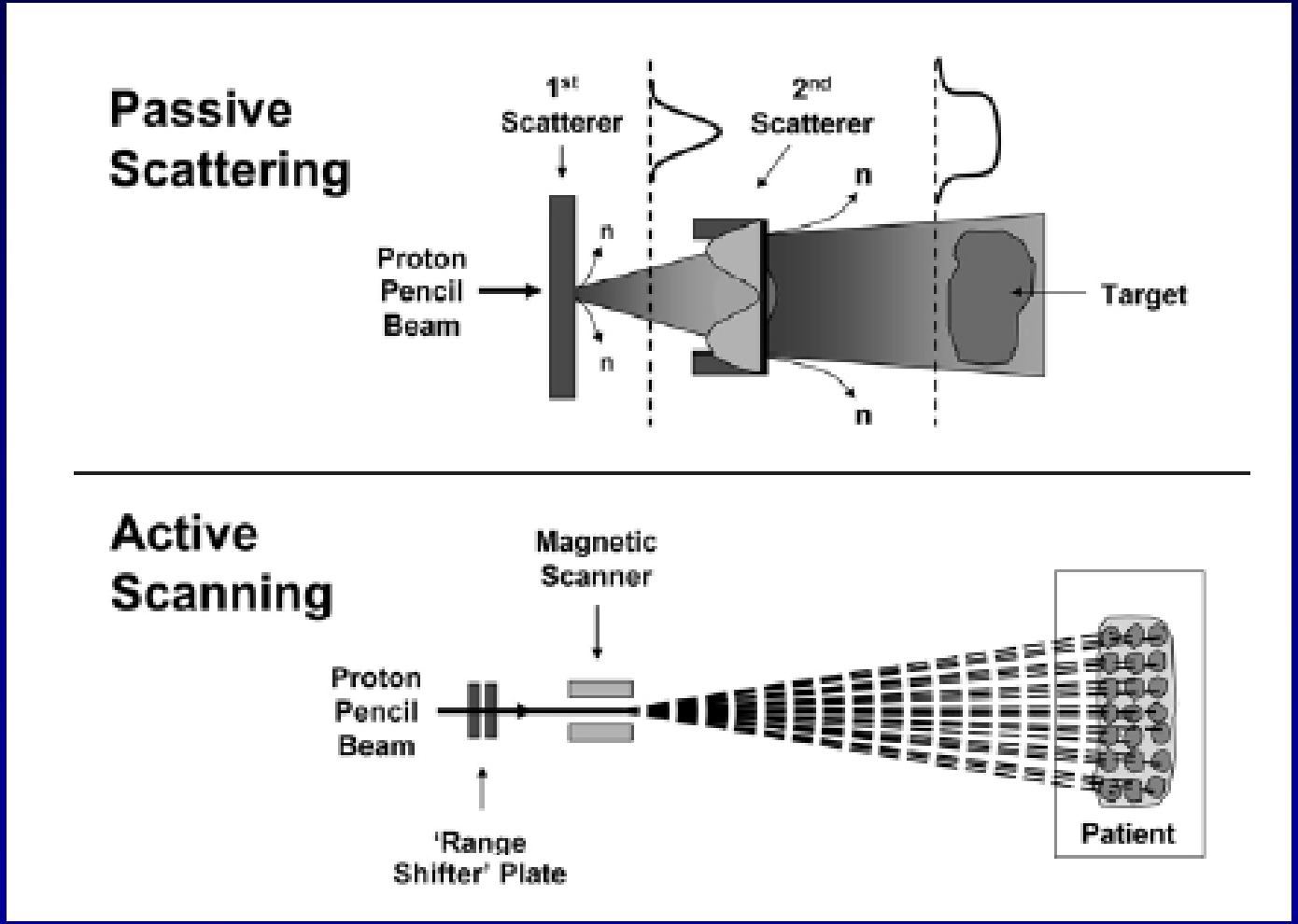


Risks of highly conformal radiation

Integral Dose

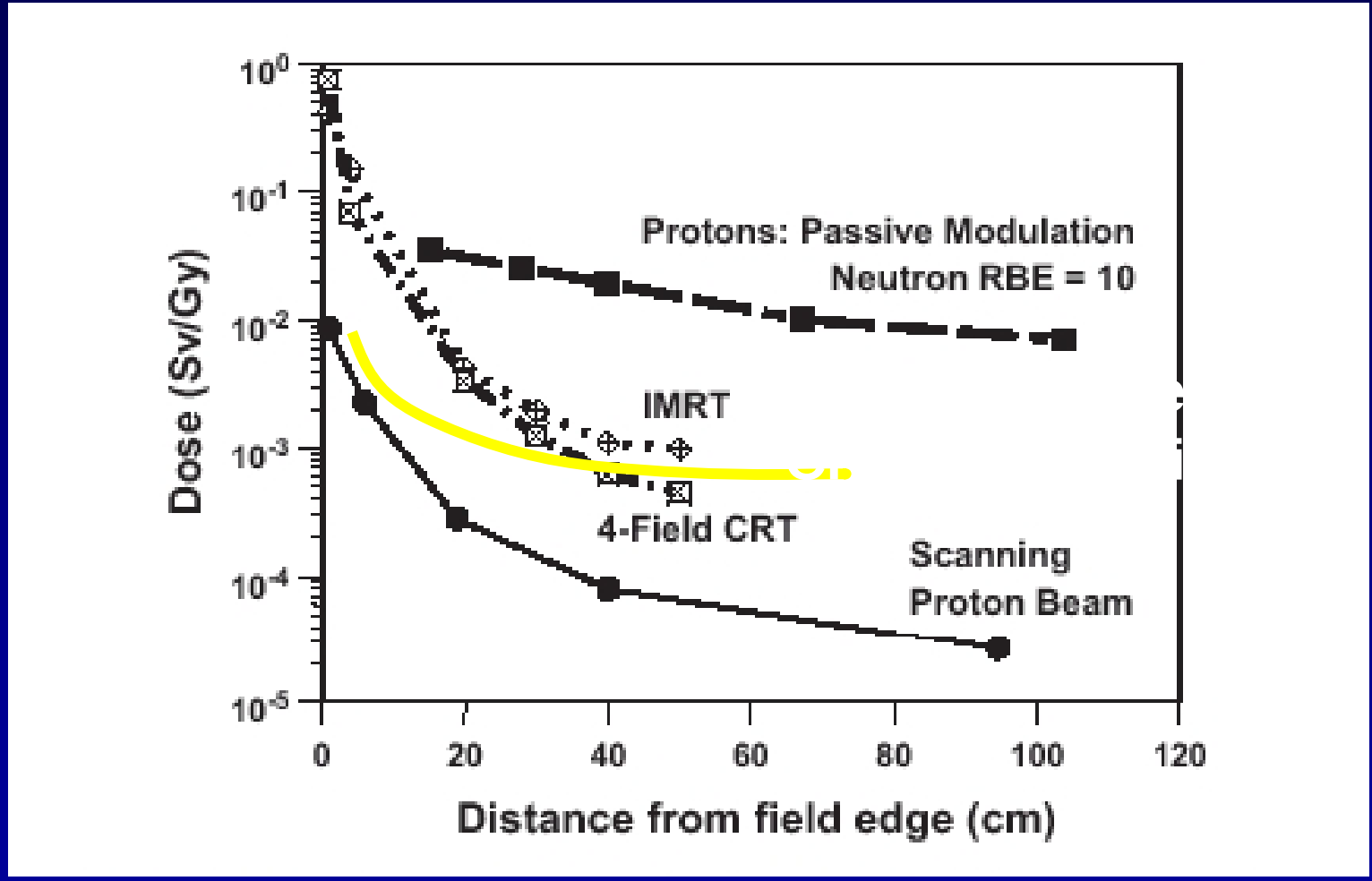


Neutron production with proton radiation



Radiation exposure from EBRT

Out of field



Where do protons fit in?

- Is the dose distribution superior to IMRT?
  - Technically yes, but clinical implications unclear
- Are they clinically more efficacious or better tolerated?
  - Not currently
- Can we afford them?
  - Maybe not
- Has treatment delivery been optimized?
  - Definitely not

Future directions

where protons may be superior

- Hypofractionation
- Stereotactic therapy
- Focal therapy
  - Dependent on improved imaging
  - As opposed to AS
- Partial prostate boost

- All of these may create a new opportunity for proton radiation to be an important and cost-effective tool for prostate cancer treatment