

A new Kind of Ray:
The last 100 Years

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A Brief History of Radiation

- Wilhelm Roentgen discovered *X-rays* on November 8, 1895, while experimenting with a gas-filled cathode tube
 - He noted an image of the bones of his hand projected on a screen when placed between the tube and the fluorescent screen
 - He wrote a carefully reasoned explanation of the phenomenon within two months



Early radiograph taken by Roentgen, January, 1896.

Brief History of Radiation Therapy

- The first patient was treated with radiation in 1896, two months after the discovery of the X-ray.
- Back then, both doctors and non-physicians treated cancer patients with radiation.
- Rapid technology advances began in the early 1950s with cobalt units followed by linear accelerators a few years later.
- Recent technology advances have made radiation more effective and precise.

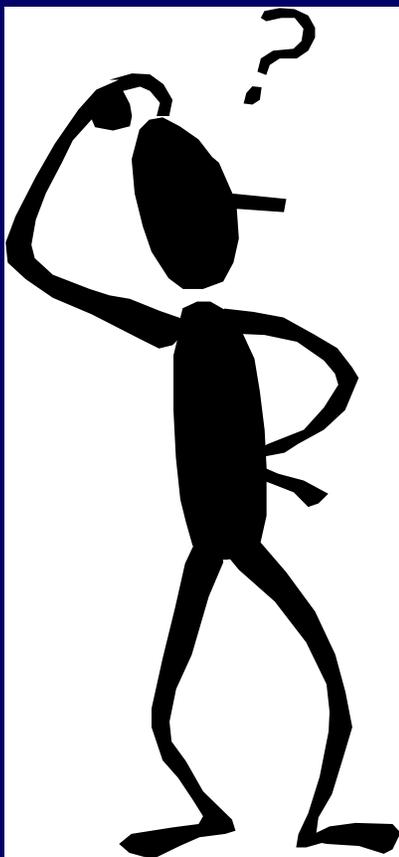


Prostate Cancer

Case presentation/ Prostate

- 60 yom with organ confined CAP T1c stage II, PSA – 10, gl 3+3 involving 1/6 cores

Questions



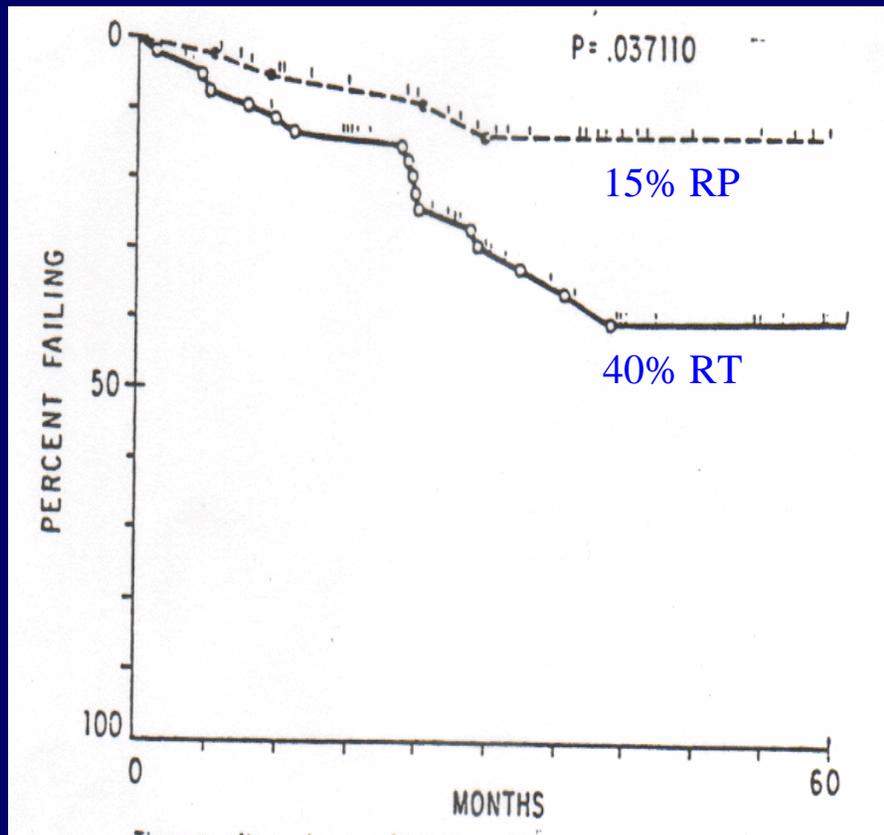
- The first debate RP vs RT for this low risk group pt
- The second debate Dose escalation with 3D RT for this pt
- 3D vs IMRT

Paulson et al 1982/ 1st debate

97 pts T1/T2 N0 CAP randomized to RP vs EBRT.

- balanced group of 4 pts to either RP or RT.
- 41 pts underwent RP.
 - either perineal or suprapubic route.
- 56 pts received EBRT
 - RT given to large pelvis 45-50 Gy, to prostate boost 20 Gy, total dose 65-70 Gy.
- Treatment failure – elevation of acid phosphatase x2, DM to bones/parenchyma.
- End point – time to first evidence of treatment failure.

Paulson et al 1982



Concl:

- Prostatectomy better than EBRT.

Flaws:

- Peculiar randomization.
- Differences in clinical stages.
- Analysis as treatment given.
- Local control not mentioned.
- Study inconclusive.

D'Amico et al 1998

- Between 1989 and 1997
 - 1872 pts with localized CAP stage T1c-T2b, retrospectively analyzed
 - **RP vs ERRT vs implant**
- Pts were stratified into risk groups
 - low risk: T1c or T2a and PSA ≤ 10 and gl ≤ 6
 - intermediate risk: T2b or PSA > 10 and ≤ 20 or gl 7
 - high risk: T2c or PSA > 20 or gl ≥ 8 .
- 1992 AJCC Staging – H&P, PSA, CT/MRI, BS, TRUS guided needle bx
 - Radiologic/bx info not used to determine clinical stage

D'Amico et al 1998

- Surgical treatment
 - RP and bilat pelvic LN sampling.
- EBRT was given with at least 10 MV and conformal 4 fld tech to 66-67 Gy
- Implant was given by Pd-103, with a peripheral loading tech to 115 Gy MPD.
- Pts in each risk groups were analyzed for time to PSA failure as a function of treatment they received.

D'Amico et al 1998

	Relative risk/5 yr bFS					
[relative to RP]	low risk		inte risk		high risk	
	RR	bFS (%)	RR	bFS (%)	RR	bFS (%)
EBRT	1.1	85	0.8	60	0.9	15
Implant	1.1	85	3.1	35	3	0
HTx+Implant	0.5	85	1.6	60	2.2	0

- Low risk pts no significant diff in outcome across all tx modalities, **RP, EBRT, Implant**
- Inter risk pts did significantly worse if managed by implant alone
- High risk pts did significantly better txed using RP or EBRT

Conclusions/ 1st debate

- Data presented indicated that all available treatment modalities may be acceptable for low risk CAP pts for PSA free survival
- However, it is possible that significant difference in QOL may exist between the treatment modalities

Pollack et al 2002/ 3DCRT 2nd debate

- 304 pts with CAP T1-3Nx/N0 randomized to
> RT dose 70 Gy vs 78 Gy.
- Median pretreatment PSA was 7.8 ng/ml, failure was defined as ASTRO consensus panel.
- RT given initially 4 flds to 46 Gy then 6 flds 3D CRT to boost, dose specified to isocenter
- No pts received neoad/adj androgen ablation
- Primary end point FFF, secondary end point DM, OS.

Pollack et al 2002/ 3DCRT

- FFF/OS results at 6 yrs

Doses	PSA	PSA	all	OS
	≤ 10	> 10	pt	all
	(%)	(%)	(%)	(%)
70 Gy	75	43	64	87
78 Gy	75	62	70	90
p value	ns	0.01	0.03	0.67

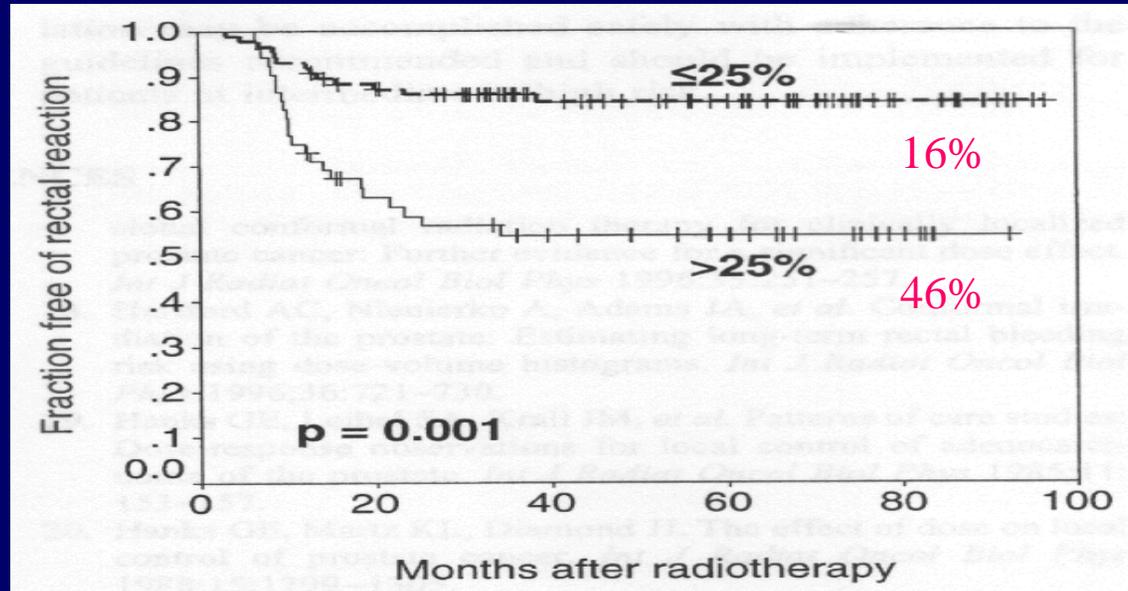
Pollack et al 2002/ 3DCRT

- Late toxicity results at 6 yrs

Doses	Rectal	Bladder
	gr \geq 2 (%)	gr \geq 2 (%)
70 Gy	12	10
78 Gy	26	10
p value	0.001	ns

Pollack et al 2002/ 3DCRT

- Gr 2 or higher late rectal complications
- Toxicity related to Volume of rectum

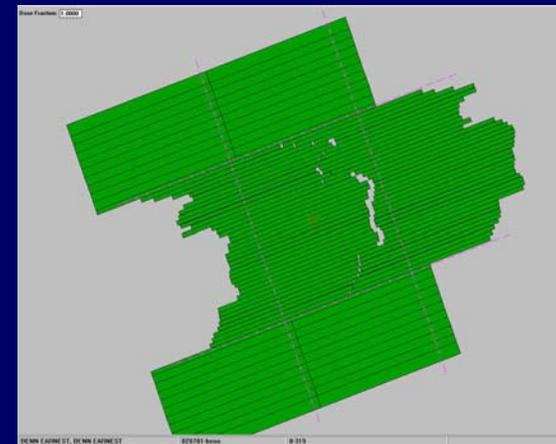
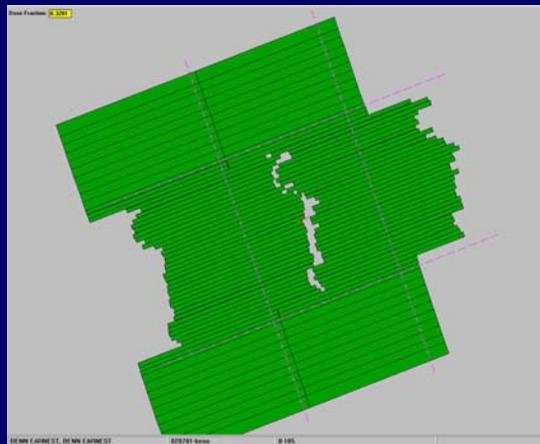
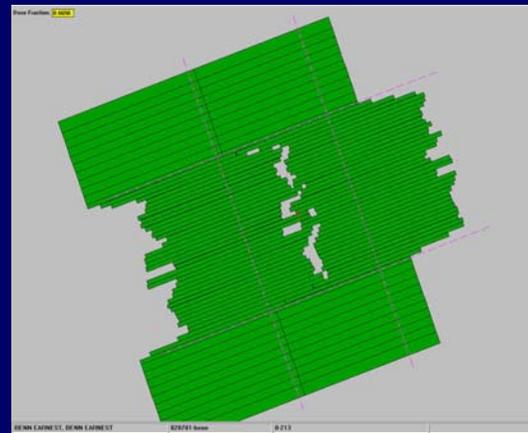
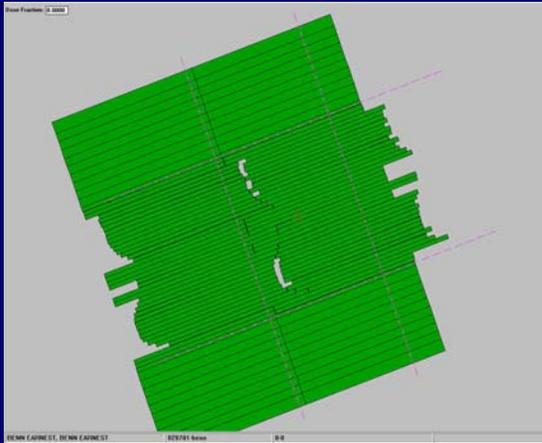


- Conclusion
 - Dose escalation 8 Gy improved FFF for prostate pts
 - However, higher dose increased rectal toxicity

Teh et al., 1999

- IMRT is a new technology in RT that delivers radiation precisely to the tumor while relatively sparing the surrounding normal tissues.
- Combines two advance concepts to deliver 3D conformal radiation
 - inverse treatment planning with computer optimization
 - computer controlled intensity modulation of the radiation beam
- Potential advantages
 - to create multiple targets
 - multiple critical avoidance
 - new accelerated fractionation scheme

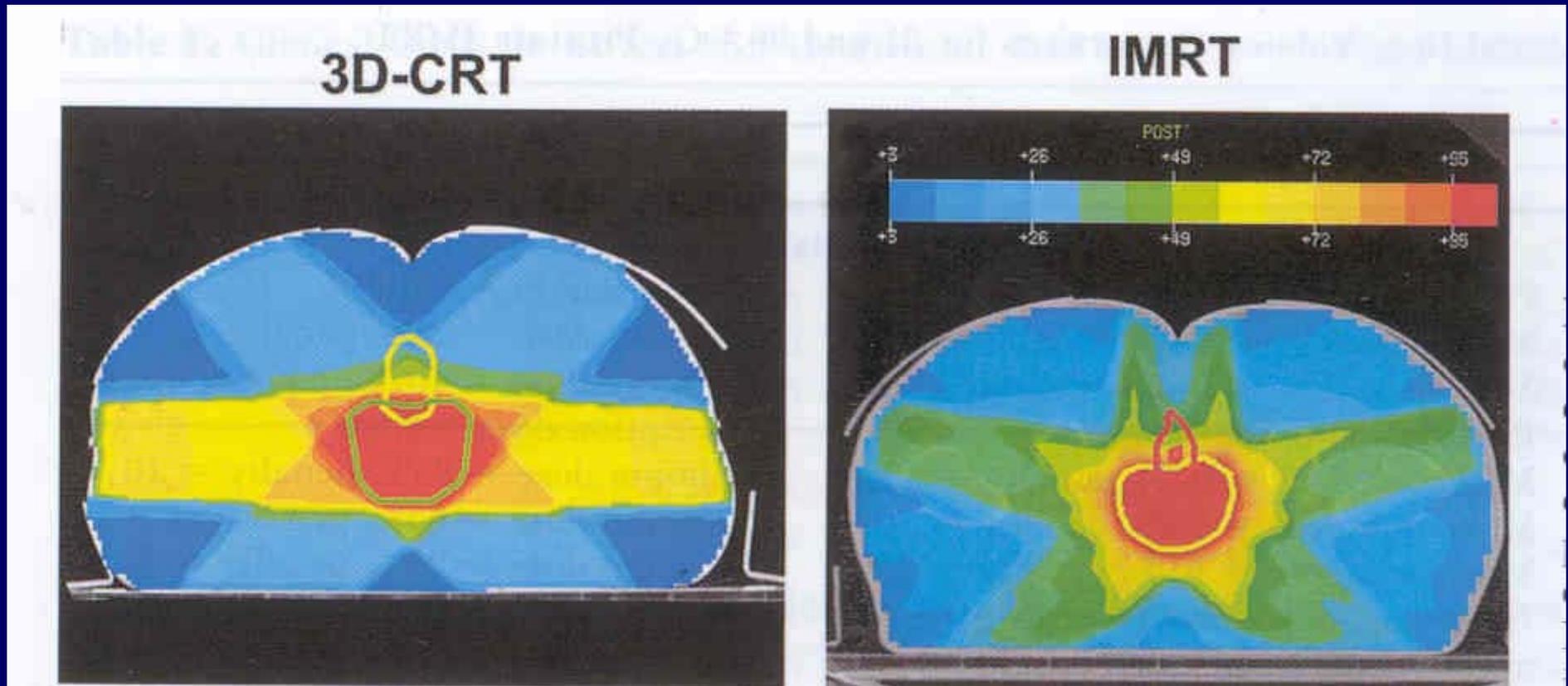
Murshed et al., 2001



Zelevsky et al 2002/ IMRT

- 1996-2001, 772 pts with clinically localized CAP txed IMRT.
- T1-2, PSA \leq 10, gl \leq 6
 - favorable - 3 present
 - intermediate - 2 present
 - unfavorable - 0-1 present
- RTOG scale to grade toxicity.
- Isocentric 5 flds, inverse plan, 15 MV, 81-86 Gy to PTV.

Zelevsky et al 2002/ IMRT



Zelevsky et al 2002/ IMRT

- Results: actuarial PSA free survival
- Median f/u 24 m (6 - 60 m)

Risk	3D CRT	3DCRT	IMRT
group	64.8-70.2 Gy	75.6-86.4 Gy	81- 86.4 Gy
	at 5 yrs (%)	at 5 yrs (%)	at 3 yrs (%)
fav	77	90	92
int	50	70	86
unfav	21	47	81

Zelevsky et al 2002/ IMRT

- Results: acute and late toxicity
- Median f/u 24 m (6 - 60 m)

Tox	acute	late	acute	late
grade	GI (%)	GI (%)	GU (%)	GU (%)
0	74	89	33	74
1	22	9	38	16
2	4	1.5	28	9.5
3	0	0.5	1	0.5

Zelevsky et al 2002/ IMRT

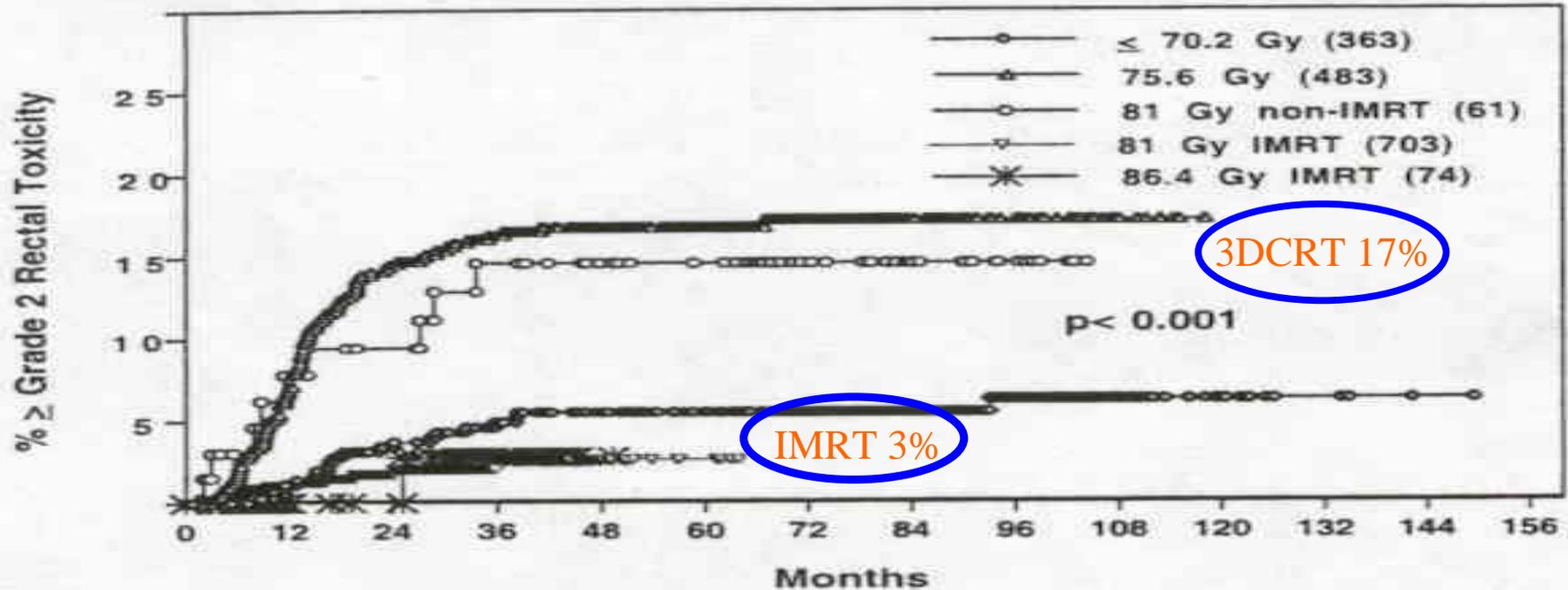


Figure 2. Actuarial incidence of grade 2 and higher late rectal toxicity according to dose and mode of treatment delivery.

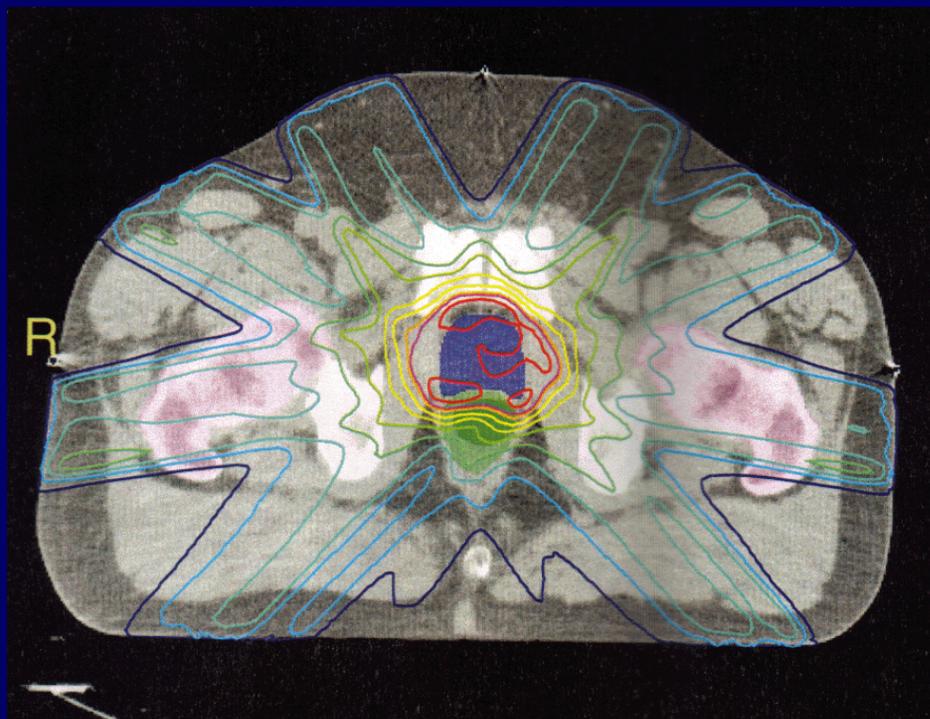
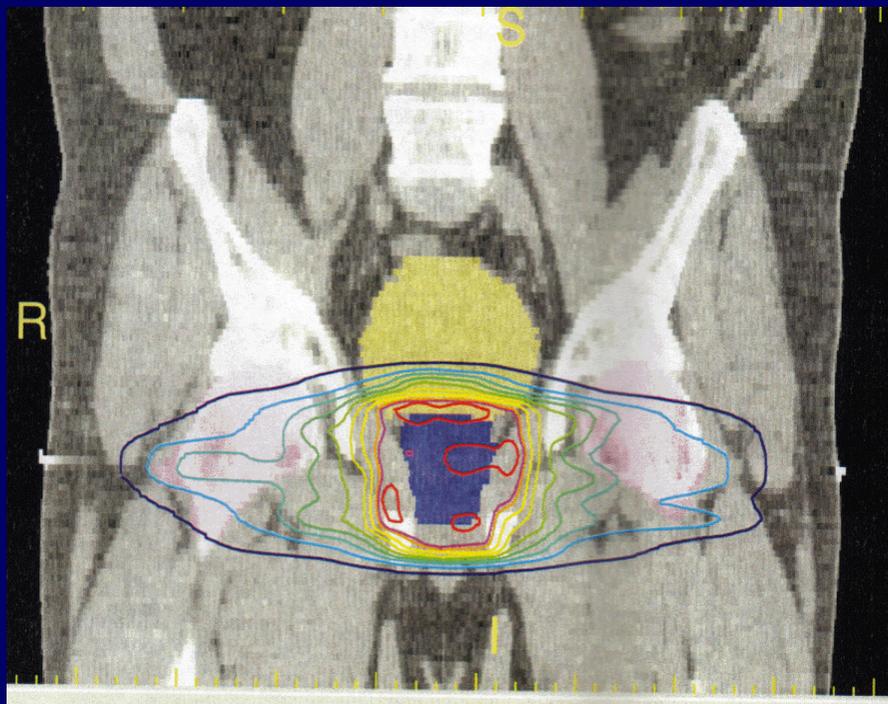
Zelevsky et al 2002/ IMRT

- Conclusions:
- Short term bFS of pts treated with IMRT is comparable with 3D CRT at similar dose level
- IMRT reduced acute and late rectal toxicity significantly compared with 3D CRT
- Report confirms the safety of high dose IMRT in a large number of CAP pts

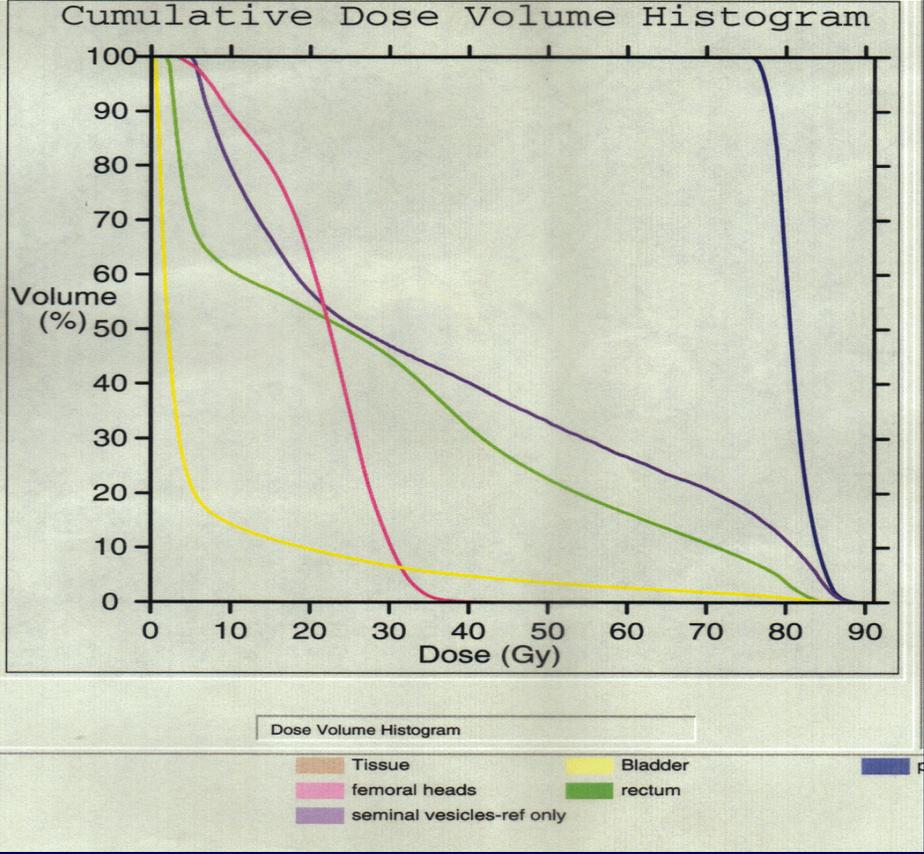
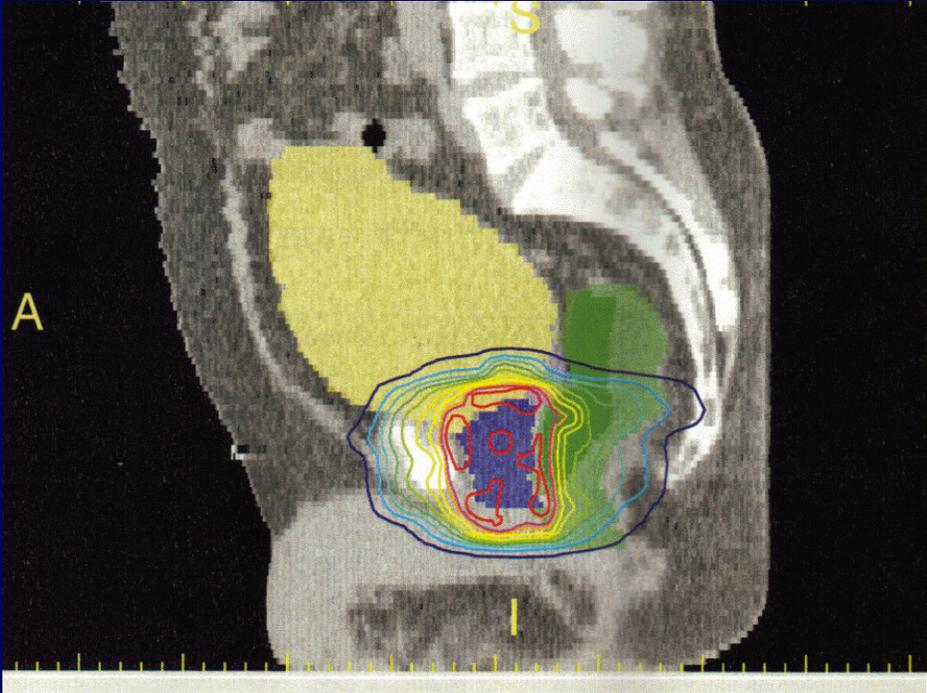
Case Presentation/ Prostate Tx

- After careful consideration all his options including RP and RT, the pt decided to proceed with RT
- He received RT to Prostate + SV to 55.8 Gy, followed by a boost dose to a final dose to 75.6 Gy, utilizing IMRT technique

Case Presentation/ Prostate Tx



Case Presentation/ Prostate Tx



Ongoing Clinical Trial

- Most reports indicate that the alpha-beta ratio is between 1 and 3. If this hypothesis is in fact true, then **hypofractionated** regimens (less frequent, larger fractions) may be more efficacious and less costly.
- To date the preliminary results from two randomized trials examining fractionation schedules for prostate cancer have been published.
 - Yeoh EE, Fraser RJ, McGowan RE, et al. *Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: early results of a phase III randomized trial.* Int J Radiat Oncol Biol Phys 2003; 55:943-955.
 - Lukka H, Hayter C, Julian JA, et al. *Randomized trial comparing two fractionation schedules for patients with localized prostate cancer.* J Clin Oncol 2005; 23:6132-6138.

Ongoing Clinical Trial



RADIATION THERAPY ONCOLOGY GROUP

RTOG 0415

**A PHASE III RANDOMIZED STUDY OF HYPOFRACTIONATED 3D-CRT/IMRT VERSUS CONVENTIONALLY
FRACTIONATED 3D-CRT/IMRT IN PATIENTS WITH FAVORABLE-RISK PROSTATE CANCER**

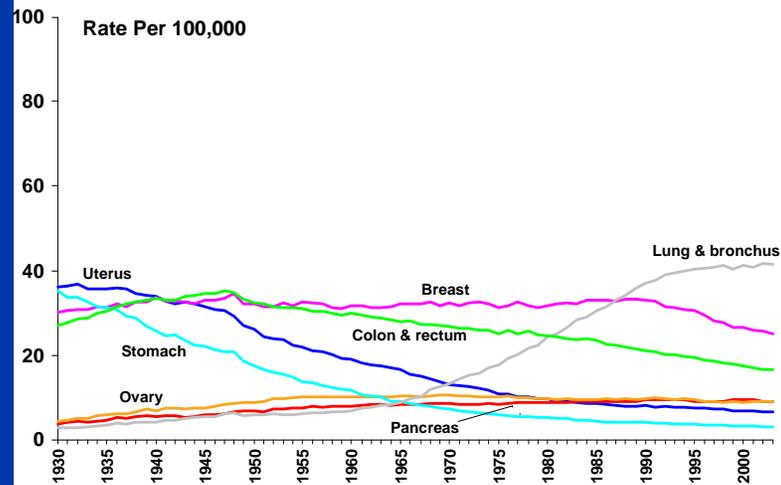
RTOG protocol/ QD IMRT over 5 weeks

- Low risk Prostate Cancer pt. receiving IMRT randomized between 8 ½ weeks vs 5 ½ weeks

SCHEMA	
S T R A T I F Y	<u>Gleason Score</u> 1. Gleason 2-4 2. Gleason 5-6
	<u>PSA</u> 1. < 4 ng/mL 2. 4- < 10 ng/mL
	<u>Radiation Modality</u> 1. 3D-CRT 2. IMRT
R A N D O M I Z E	<u>Arm 1 (Minimum PTV prescription)</u> 3D-CRT or IMRT: 73.8 Gy in 41 fractions
	<u>Arm 2 (Minimum PTV prescription)</u> 3D-CRT or IMRT: 70 Gy in 28 fractions

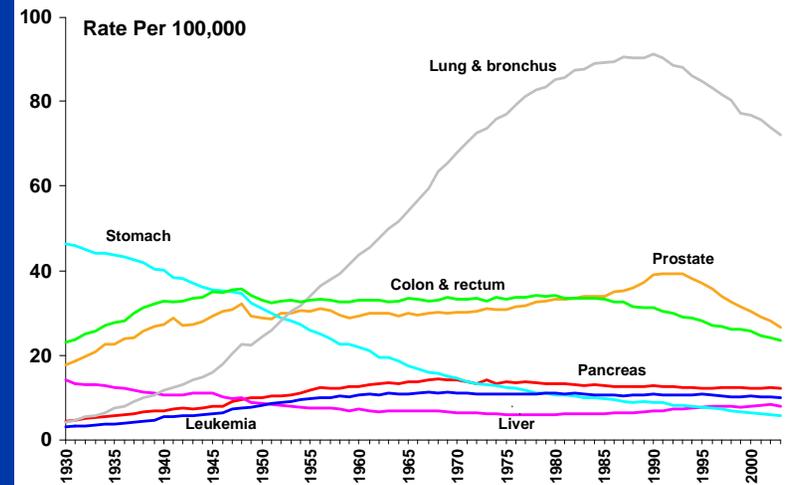
Cancer death rates 1930-2003

Cancer Death Rates*, for Women, US, 1930-2003



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes 1960-2003, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

Cancer Death Rates*, for Men, US, 1930-2003



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes 1960-2003, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

Conclusions/ Prostate

- All available treatment modalities such as RP, EBRT, or Implant may be acceptable for low risk CAP pts
- RT dose escalation with IMRT improves bFS in prostate cancer pts

Conclusions/ Prostate

- IMRT reduced GI toxicity in prostate cancer pts
- Phase III clinical trial underway to determine
 - whether hypofractionated IMRT provides equivalent local tumor control compared to conventional RT in the local management of low risk Prostate cancer.
 - We are now enrolling patients with low risk Prostate cancer in local clinical trial at the local hospital in Panama City, FL.

Conclusions



- IMRT is the latest radiation technique
- X-rays have come a long way in last 100 yrs, now actively contributing to cure of cancers

The End



Thanks

- Dr. Buchholz, MD Anderson Can Cnt
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