Advances in External Beam Radiotherapy for Prostate Cancer

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External Beam Radiotherapy 2013

- High dose radiotherapy as a critical ingredient for long term tumor control in prostate cancer.

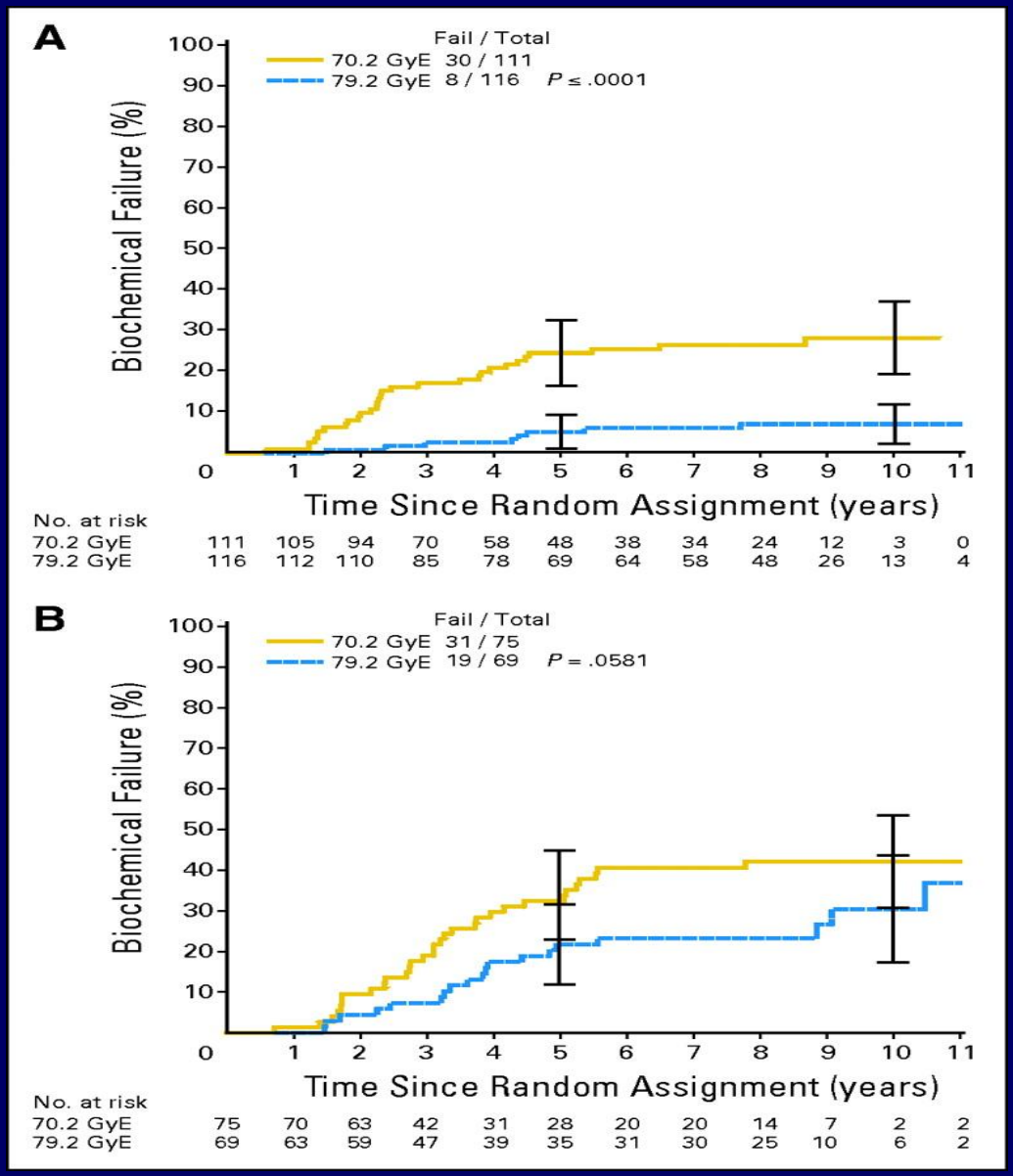
- More precise and accurate ways of delivering high radiation doses have resulted in ability to deliver high doses **more safely**.
  - IMRT (intensity modulated radiotherapy)
  - IGRT (image-guided radiotherapy)
  - SBRT (stereo-tactic body radio-surgery)

- Use of androgen deprivation therapy for intermediate and high risk disease has further improved long-term tumor control outcomes.

Randomized Trials of Dose Escalation with EBRT

Series	Randomization	Outcome	Advantage
Pollack (2002)	78 Gy vs 70 Gy	70% vs 45%	Intermediate Risk
Zietman (2006)	79.2 vs 70.2 Gy (protons)	80% vs 60%	Low and Int Risk
Peeters (2006)	78 Gy vs 68 Gy	64% vs 54%	Intermediate Risk
Dearnelay (2007)	74 Gy vs 64 Gy (with ADT)	85% vs 79%	All risk groups

Dose Escalation Advantage for Favorable Risk Disease
Zietman et al JCO 2010



Favorable Risk

Intermediate Risk

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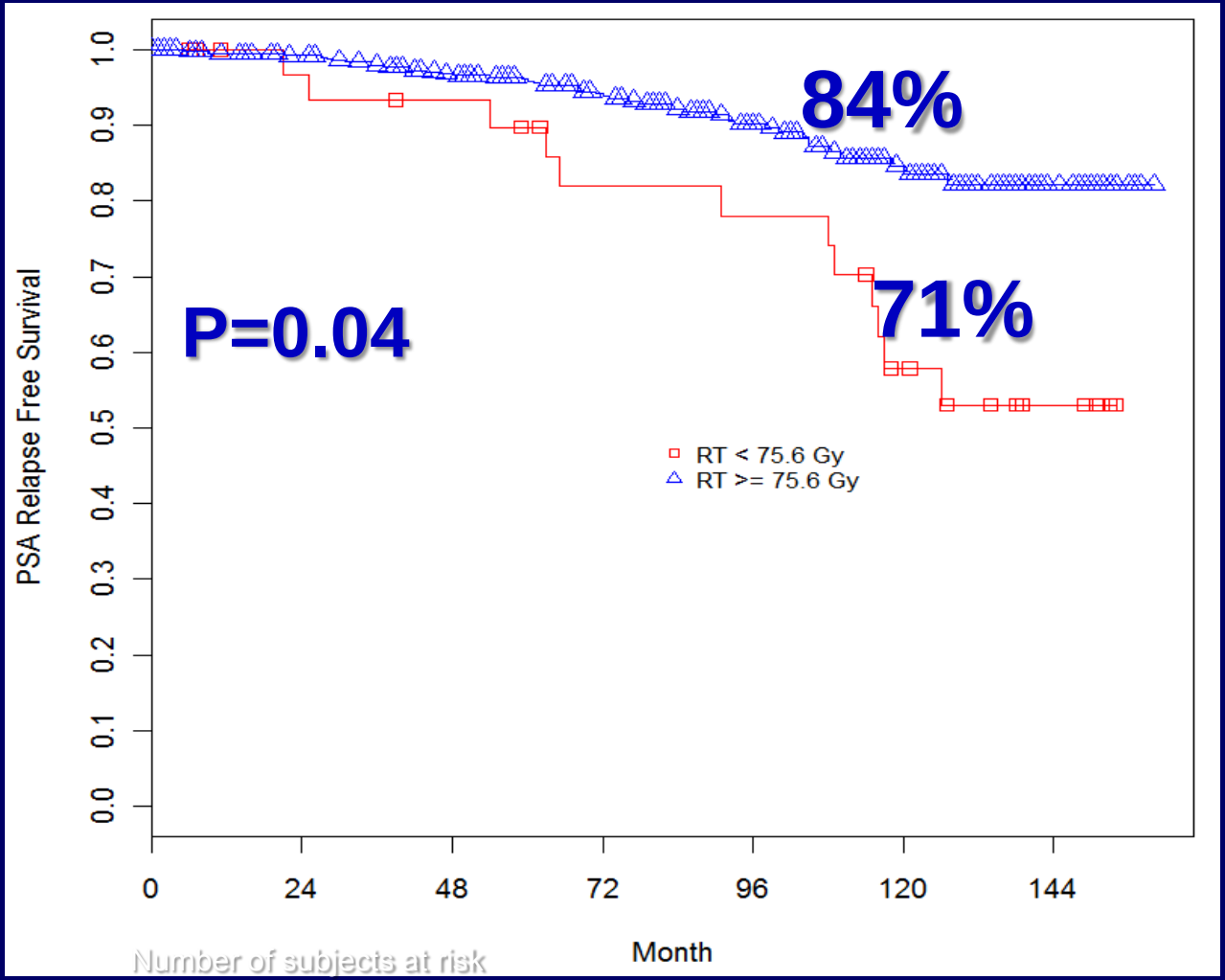
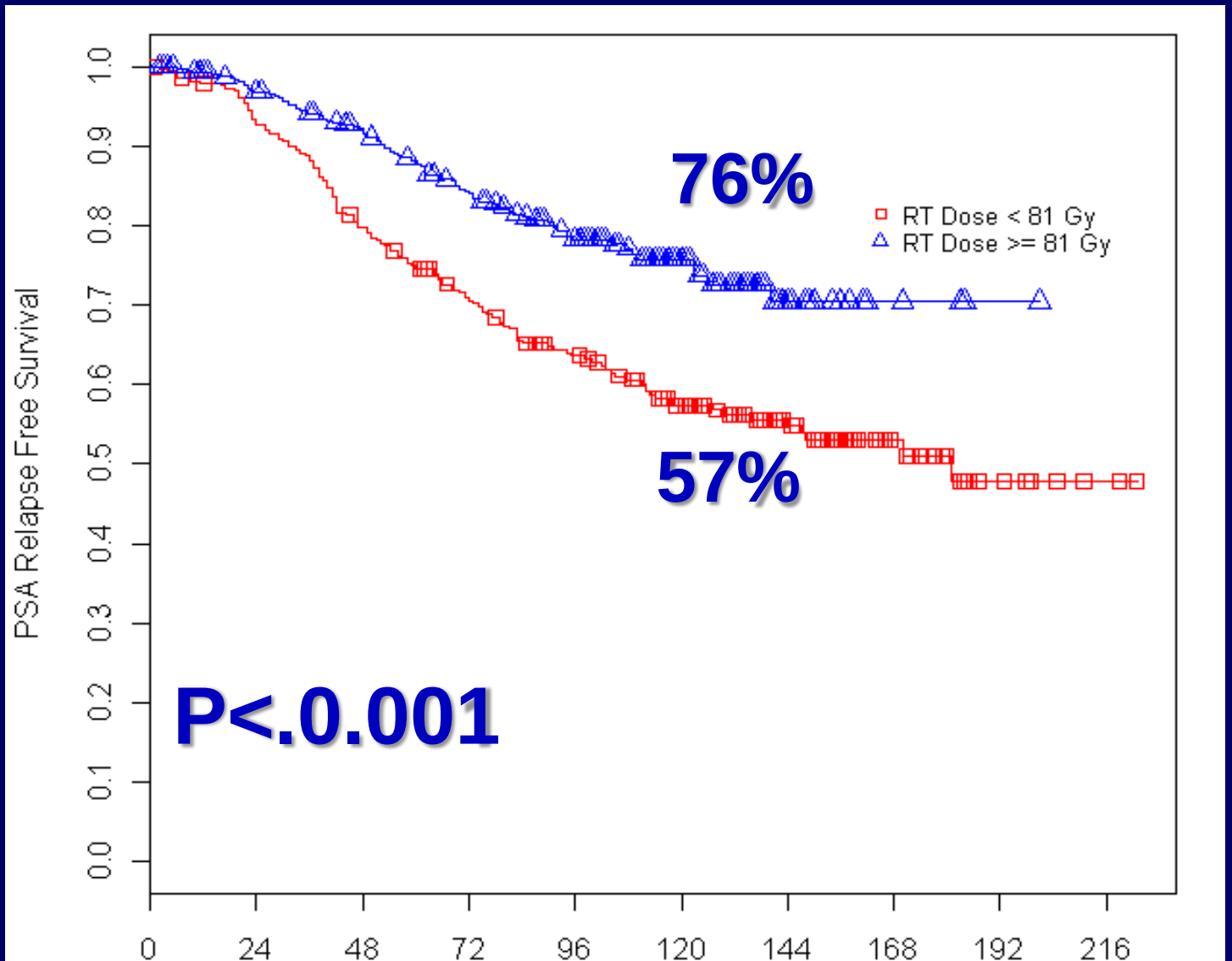
PSA RFS for Low Risk >=76. Gy versus < 75.6 Gy

(Zelefsky et al Eur Urol 2011)



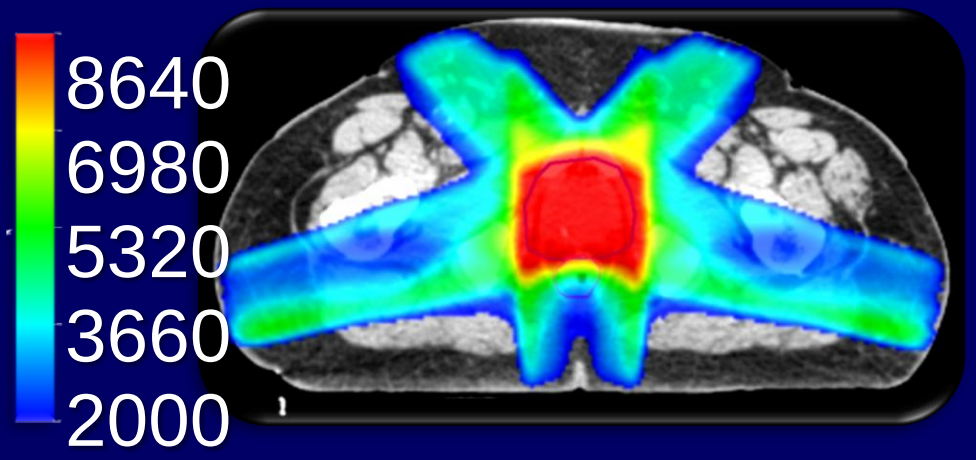
PSA RFS for Intermediate Risk >=81 Gy versus < 81 Gy

(Zelefsky et al Eur Urol 2011)

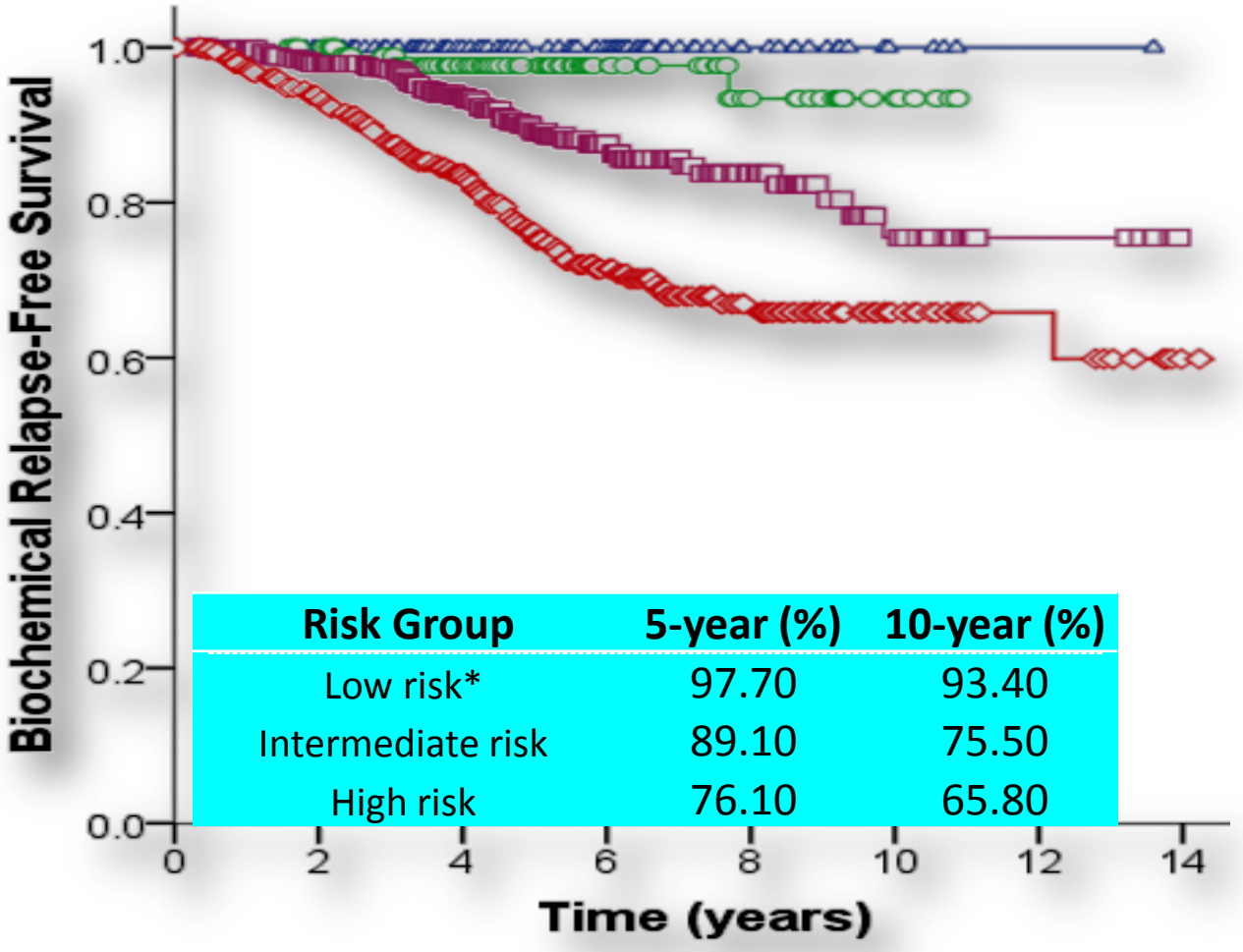


86.4 Gy Delivered to Prostate via IMRT

- Mean PTV 87.4 Gy
- D Max 95.1 Gy
- **D95 82.5 Gy**
- **D90 86.1 Gy**
- D75 88.3 Gy
- D50 89.2 Gy
- D05 91.4 Gy

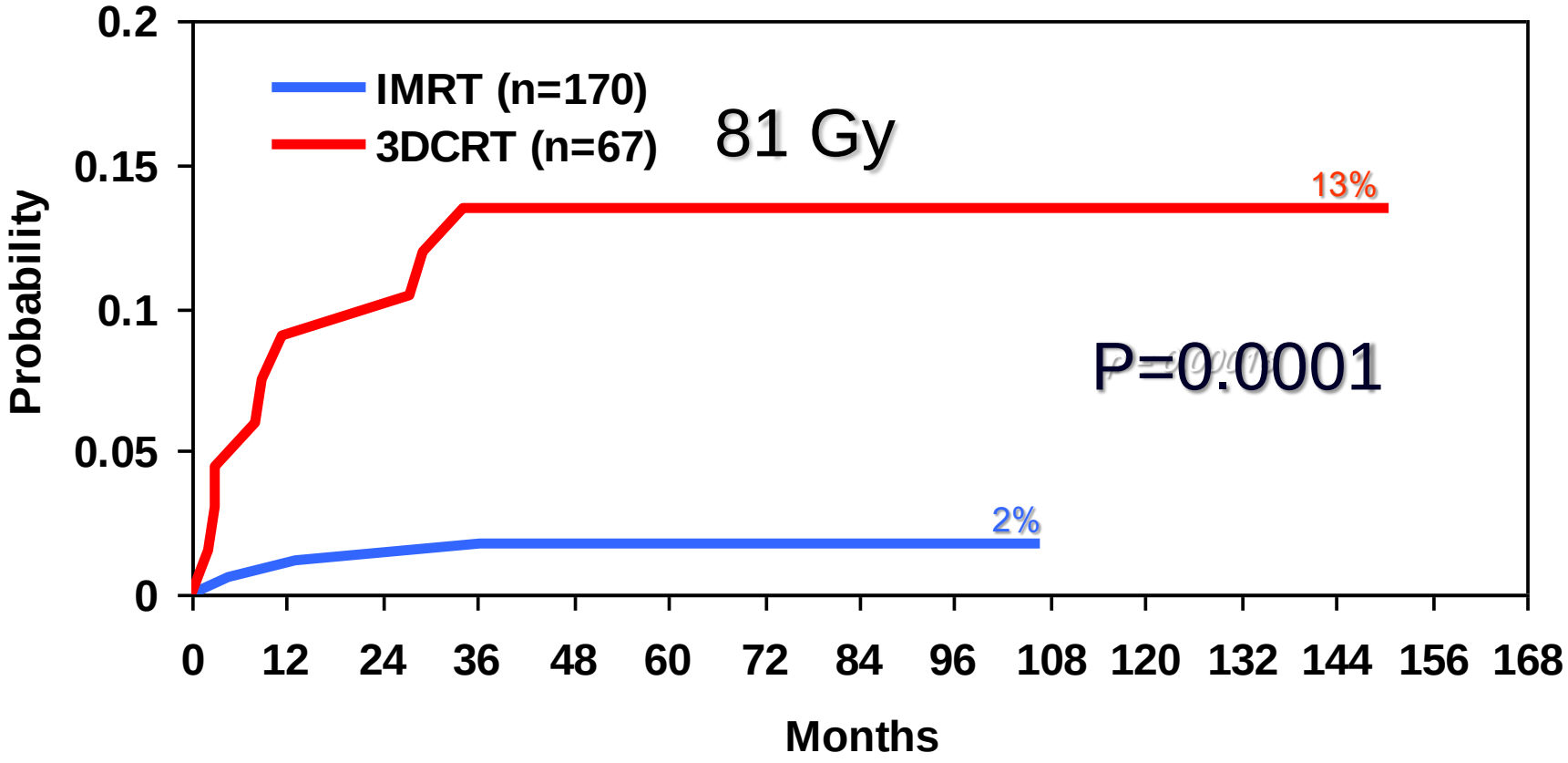


Outcome of 1002 Patients Treated with 86.4 Gy IMRT (Spratt et al IJROBP 2012)



Risk Group	5-year (%)	10-year (%)
Low risk*	97.70	93.40
Intermediate risk	89.10	75.50
High risk	76.10	65.80

Late Grade 2 GI Toxicity Development
Median Follow-Up 8 years
(Zelefsky et al J Urol 2006)



Summary of Long Term Toxicity of High Dose IMRT: MSKCC 2013

- Grade 2 urinary (frequency/urgency)- 15%-20%
- Grade 3 urinary (urethral stricture)- 2%

- Grade 2 rectal (bleeding/proctitis): 2%
- Grade 3 rectal (ulceration/significant bleeding): <1%

- Erectile Dysfunction: 30-40% @ 5 years
  - Dry ejaculate in 90% of patients

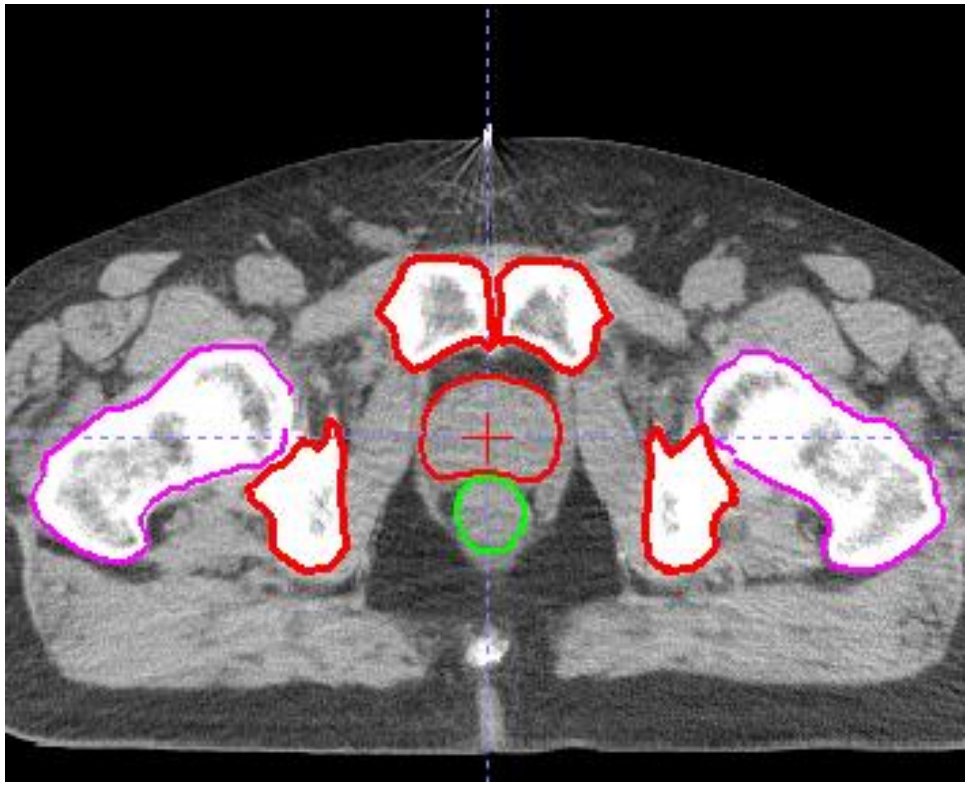
IGRT: Image Guided Radiotherapy
Further Improving on the Accuracy of Therapy

- IMRT accuracy is limited by prostate motion which changes the prostate position from day to day and even during the time when the actual radiation is being delivered.

- Placement of fiducial markers within the prostate via TRUS guidance more routine to correct daily for positional changes of the prostate.

- Such approaches are revolutionizing the way radiotherapy is being delivered
  - Tighter margins can be used
  - Less normal tissue exposure to the high doses of RT

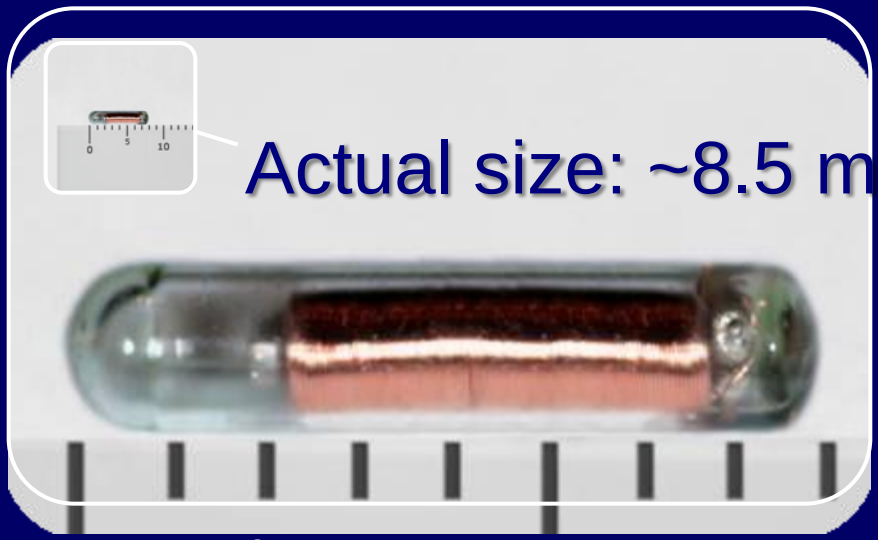
Uncertainties in Prostate Cancer Targeting



- CT images acquired with an in-room CT-on-rails system over the course of radiotherapy
- Patient positioned for daily CT and treatment using immobilization and triangulation

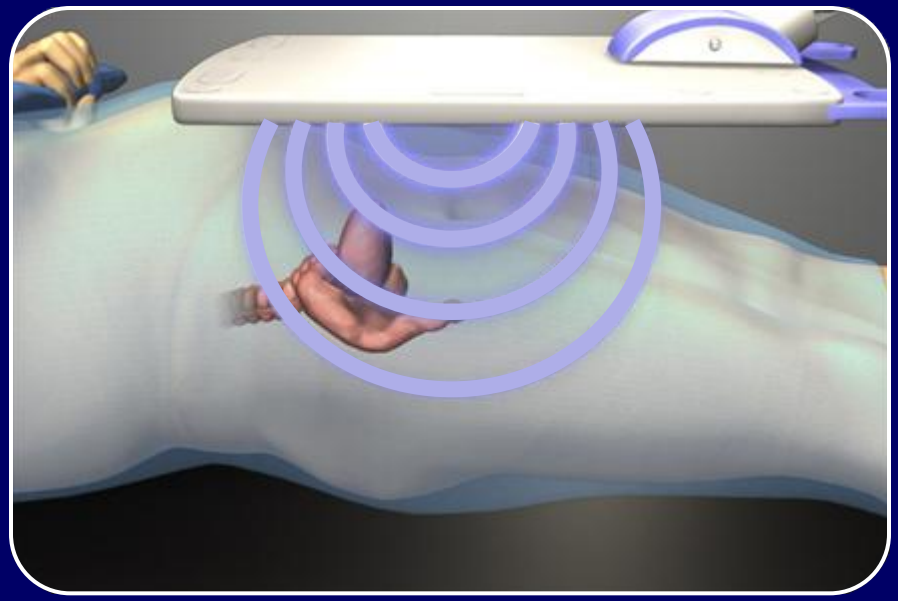
Dong & Mohan, MDACC, 2006

Calypso for Real Time Target Tracking During the Actual Treatment

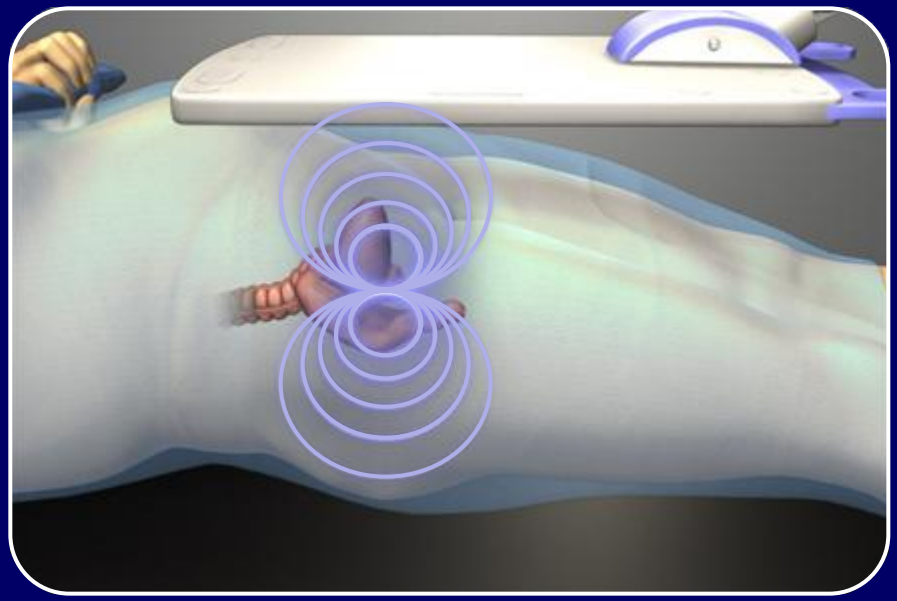


Beacon® Electromagnetic Transponder

Electromagnetics Locate and Track Continuously

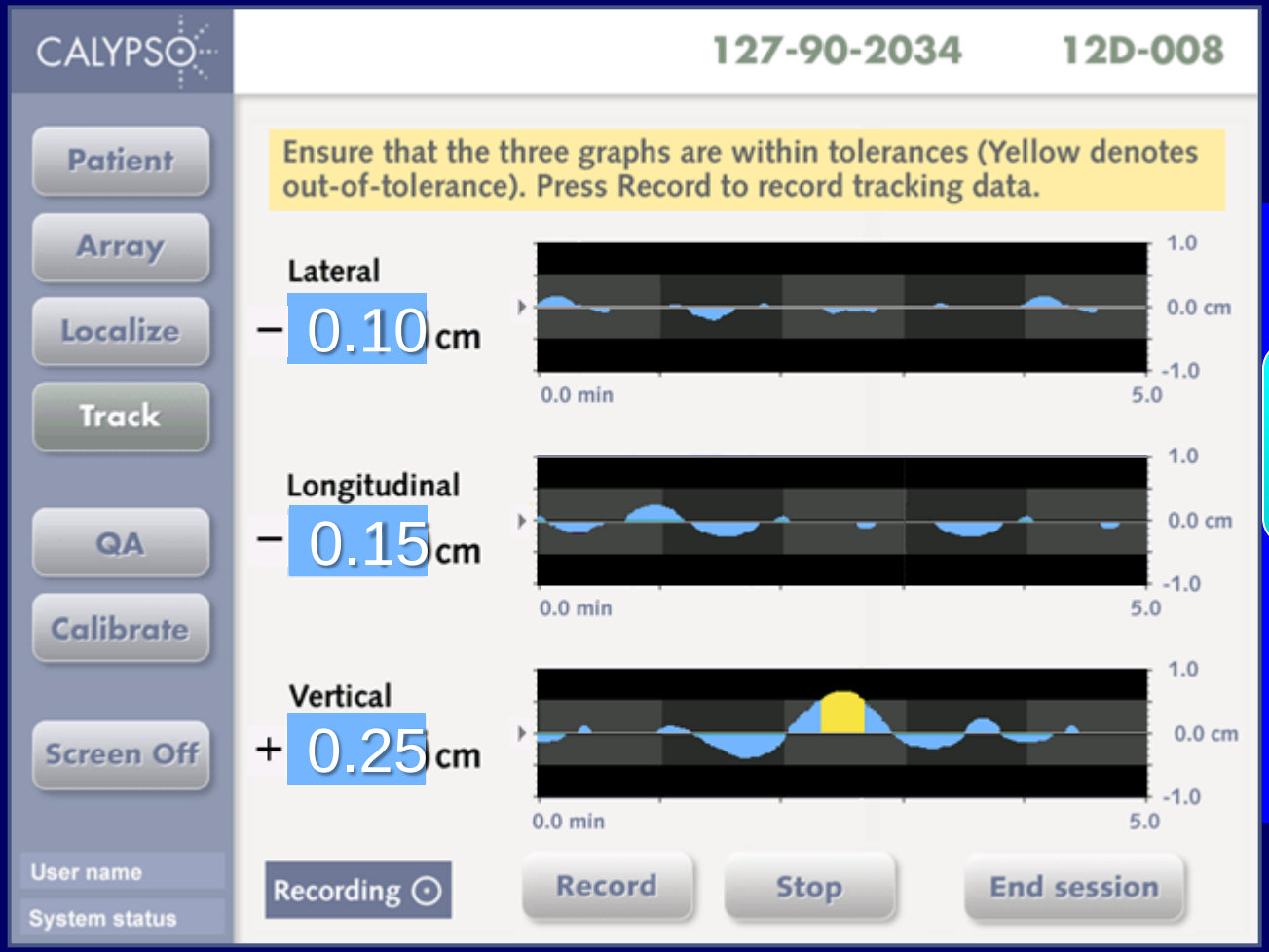


Step 1



Step 2

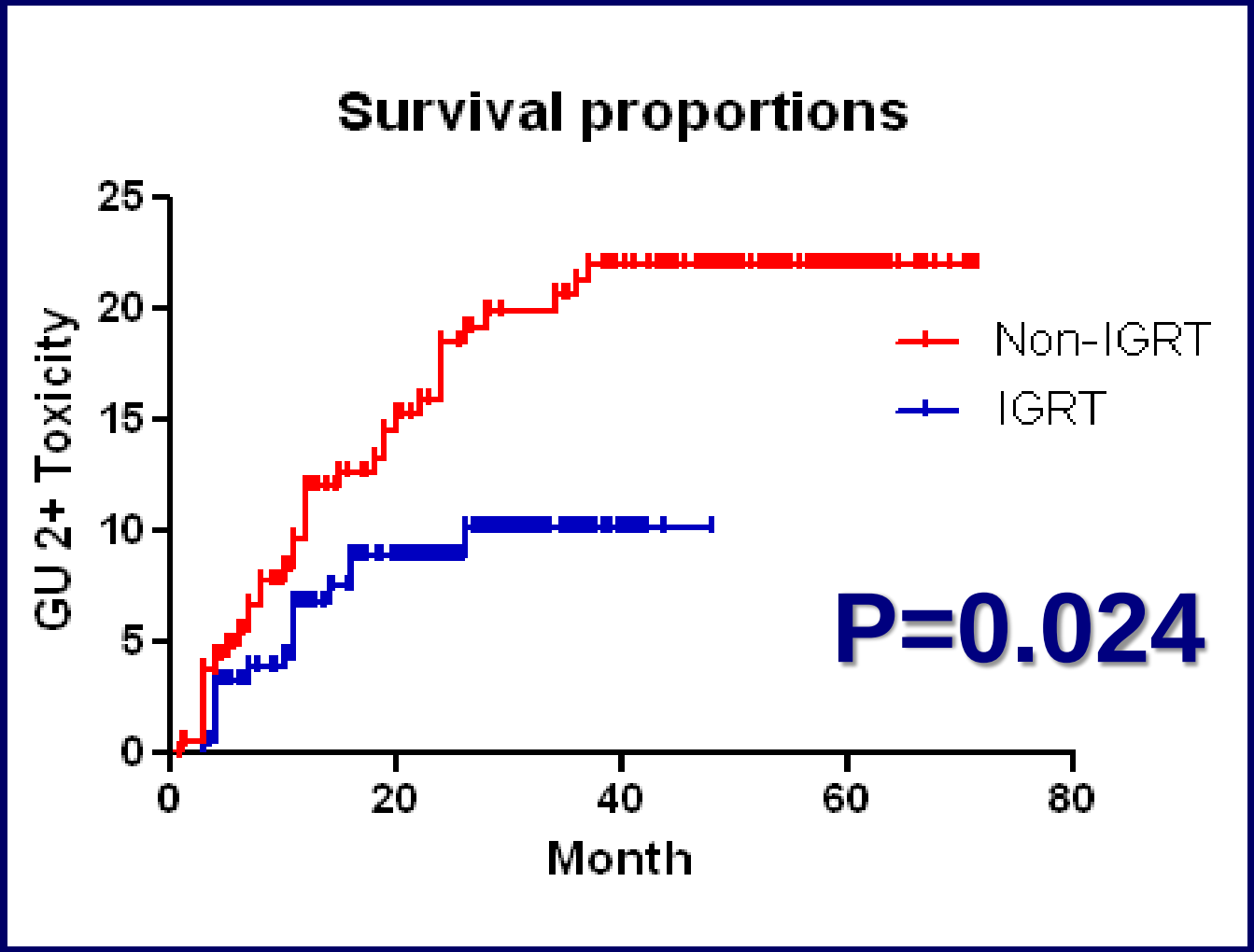
Monitoring Motion DURING the Radiation Treatment



MSKCC Threshold > 2 mm to stop the beam

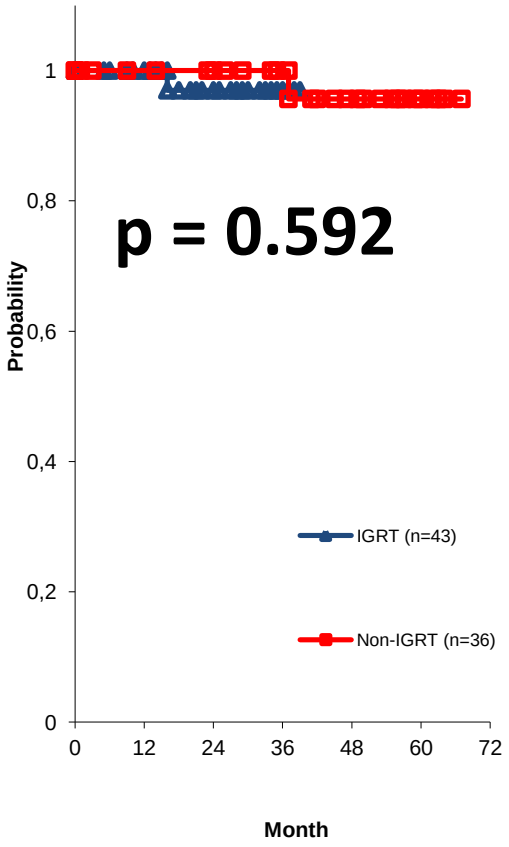
Lower Urinary Toxicity with IGRT Compared to IMRT

(Zelefsky et al Int J Radiat Oncol Biol Phys- 2012)

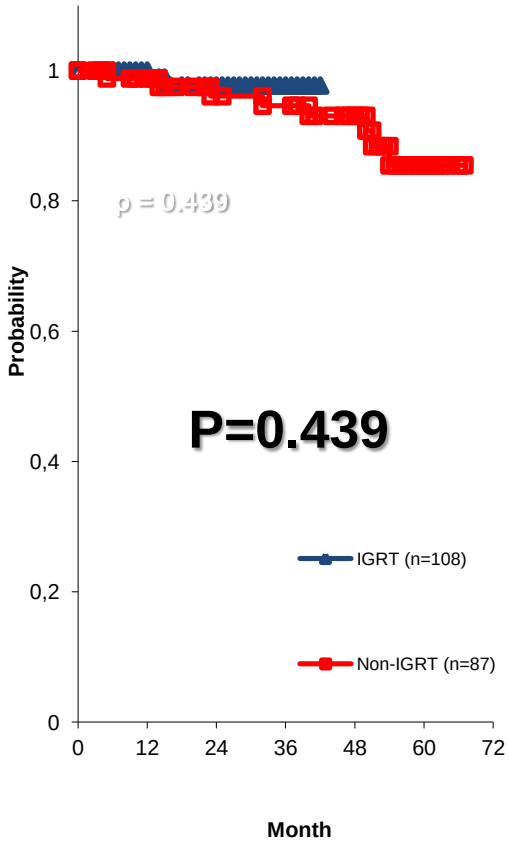


Improved PSA Control for High Risk Patients with IGRT

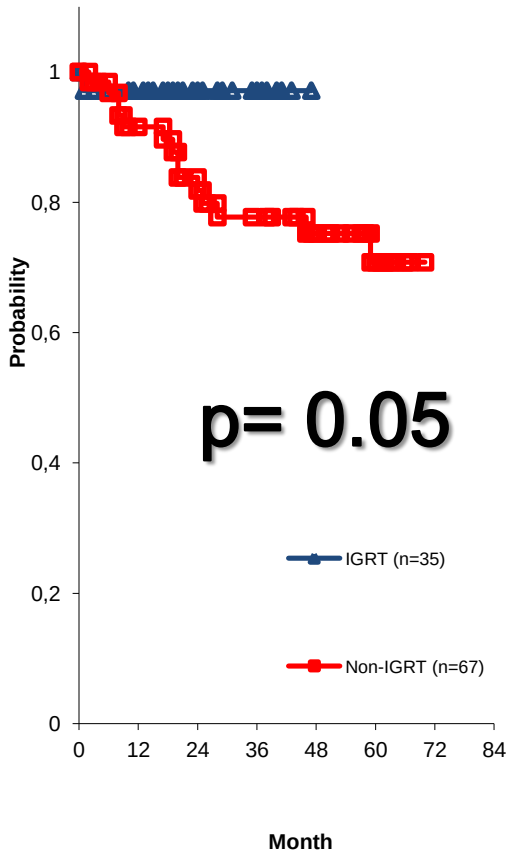
Low Risk



Intermediate Risk



High Risk



(Zelefsky et al Int J Radiat Oncol Biol Phys- i2012

Ultra-Hypofractionation for Prostate Cancer Therapy

- 5 treatments over 1.5 weeks instead of 50 treatments in 10 weeks
- Accuracy with targeting the prostate during the actual treatment
- Tighter margins meaning less inclusion of normal tissues
- Higher dose in shorter period of time thought to cause greater biological damage inside the tumor

Ultra-Hypofractionated RT Tumor Control Outcomes

Study	#	Dose/Fx	Fx	Total Dose	Median F/u (mo)	PSA Control
Virginia Mason (2010)	40	6.7	5	33.5 Gy	41	90%
Stanford (2009)	41	7.25	5	36.25 Gy	33	100%
Naples (2009)	112	7-7.25	5	35-36 Gy	24	99%
Winthrop (2010)	304	7-7.25	5	35-36 Gy	30	99%
Boike (2011)	45	9-10 Gy	5	45-50 Gy	30	100%
Georgetown (2013)	100	7-7.25	5	35-36 Gy	27	99%

Ultra-Hypofractionated RT-Toxicity Outcomes

Study	Dose/	Median F/u (mo)	Late GI Toxicity	Late GU Toxicity
King et al 2009	36.25Gy	33	48% G1-G2	65% G1-G2; 5% G3
Katz et al 2010	35 Gy	30	9% G1/G2	9% G1/G2 0.5%- G3
Bolzicco et al 2010	35 Gy	20	2.2% G-2	9% G1/G2 2.2%- G3
Freeman et al (2010)	36.25 Gy	60	15.5% G1-G2	32% G1/G2 2.5%- G3
King et al 2012	36.25 Gy	32	16% G1-G2	28% G1/G2 3.5%- G3

Ongoing Phase I Dose Escalation Study at MSKCC

- Ultra-hypofractionated IGRT Phase I dose escalation study
  - 650 cGy x5- accrual completed
  - 700 cGy x 5- accrual completed
  - 750 cGy x 5- accrual nearly completed
  - 800 cGy x 5
  - 850 cGy x 5
- Primary endpoint is toxicity
- Secondary endpoints included PSA tumor control and 2-year biopsy outcomes
- Eligibility includes IPSS< 17, Favorable/Intermediate Risk, no prior ADT

Intermediate Risk Disease

New Perspectives in Defining this Category of Risk Group

Intermediate Risk Prostate Cancer

- NCCN Intermediate Risk Factors
  - Clinical stage T2b-c
  - Gleason score 7
  - PSA 10-20
- Multiple intermediate risk factors may be classified as high risk disease
- Optimum therapy is controversial

Randomized Trials of Short Term ADT with Intermediate Risk Prostate CA

- RTOG 94-08 (Jones NEJM 2011)
  - 10 yr OS: 62% vs 57%, p = 0.03
  - Benefit driven by intermediate risk patients
- DFCI Trial (D'Amico JAMA 2008)
  - 8 yr OS: 74% vs 61%, p=0.01
  - ~75% of patients were intermediate risk

Can Dose Escalation Replace Short Term ADT?

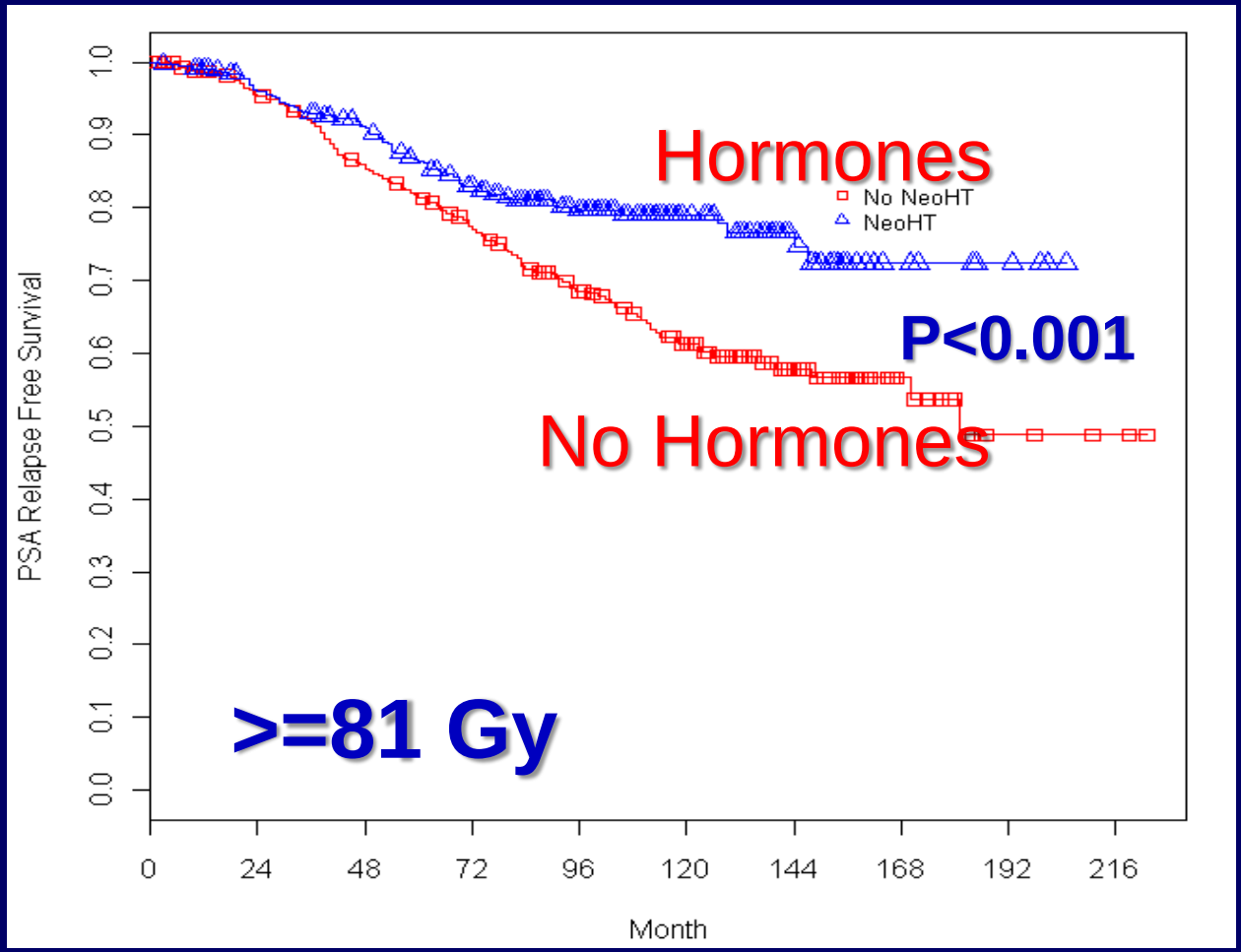
- Low Doses Used in Both Trials
  - RTOG 94-08: ~63 Gy to 95% isodose line
  - DFCI Trial: 70.4 Gy to 95% isodose line
- Dose Escalation Trials
- Is ADT necessary in the dose escalation era?

Adverse Sequelae of ADT

- Adverse Quality of Life Sequelae
  - Hot flashes, fatigue, sexual dysfunction, decreased libido, depression
- Adverse Medical Sequelae
  - Weight gain, muscle loss, diabetes
  - Anemia
  - Osteoporosis
  - Increased cardiovascular morbidity and mortality is controversial

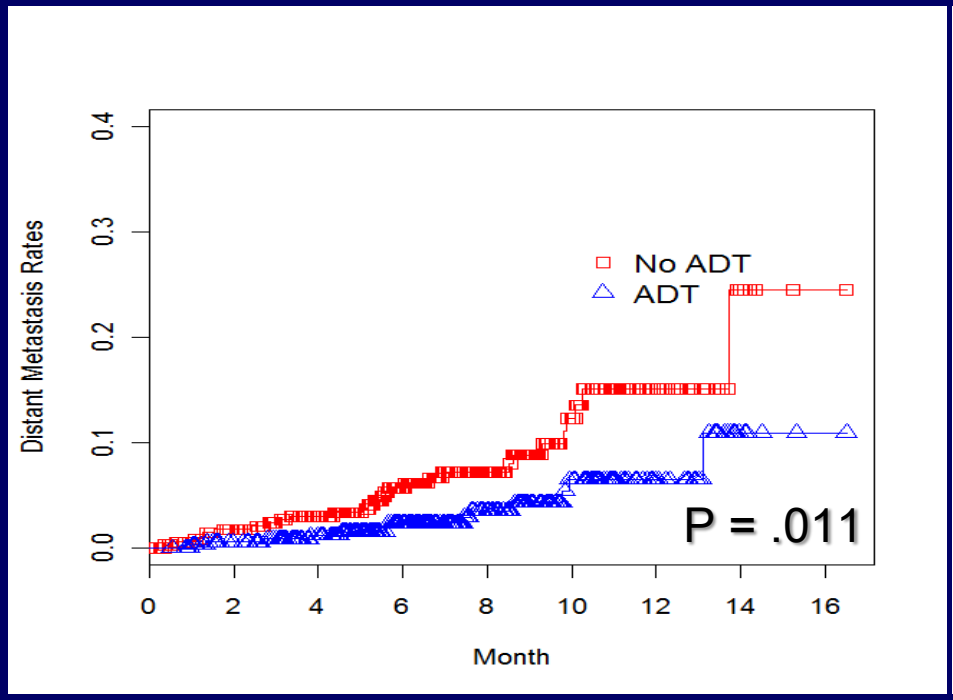
Improved Outcomes with SHORT COURSE ADT in Intermediate Risk Patients Treated with Dose Escalation

(Zumsteg et al IJROBP 2012- MSKCC)

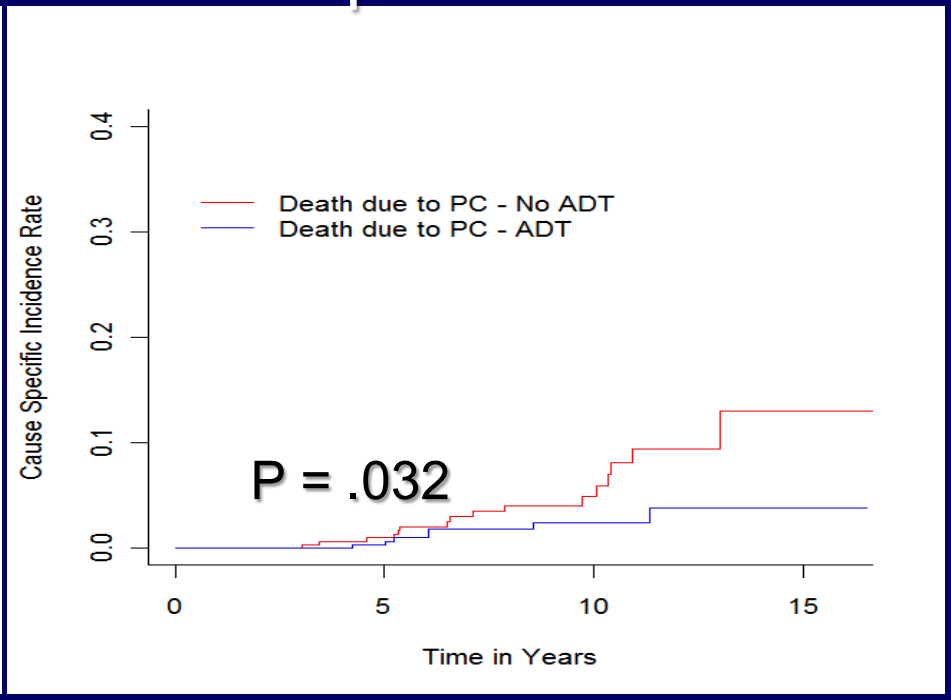


Impact of Short Course ADT on DMFS Prostate Cancer Death for Intermediate Risk Patients (Zumsteg et al IJROBP 2012)

DMFS



Cause-Specific Survival



MSKCC Treatment Algorithm for Intermediate Risk Prostate Cancer

	Favourable intermediate-risk prostate cancer*	Unfavourable intermediate-risk prostate cancer†
Clinical characteristics	One intermediate risk factor Gleason score of 3+4=7 or less <50% positive biopsy cores	Several intermediate risk factors[57] Gleason score of 4+3=7[14] ≥50% positive biopsy cores[11]
Recommended radiation options	Dose-escalated external beam radiotherapy alone Brachytherapy alone in select cases (eg, ≤3 positive cores, none with >50% involvement)	Dose-escalated external beam radiotherapy and short-term androgen deprivation therapy Combined brachytherapy and external beam radiotherapy with or without short-term androgen deprivation therapy

*All these criteria are required. †Any of these criteria can be met.

Table 5: Memorial Sloan-Kettering Cancer Center treatment algorithm for definitive radiotherapy in patients with intermediate-risk prostate cancer

Zumsteg & Zelefsky, Lancet Oncology 2012

External Beam Radiotherapy 2013

- High dose radiotherapy as a critical ingredient for long term tumor control.

- More precise and accurate ways of delivering high radiation doses have resulted in ability to deliver high doses more safely.
  - IMRT (intensity modulated radiotherapy)
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