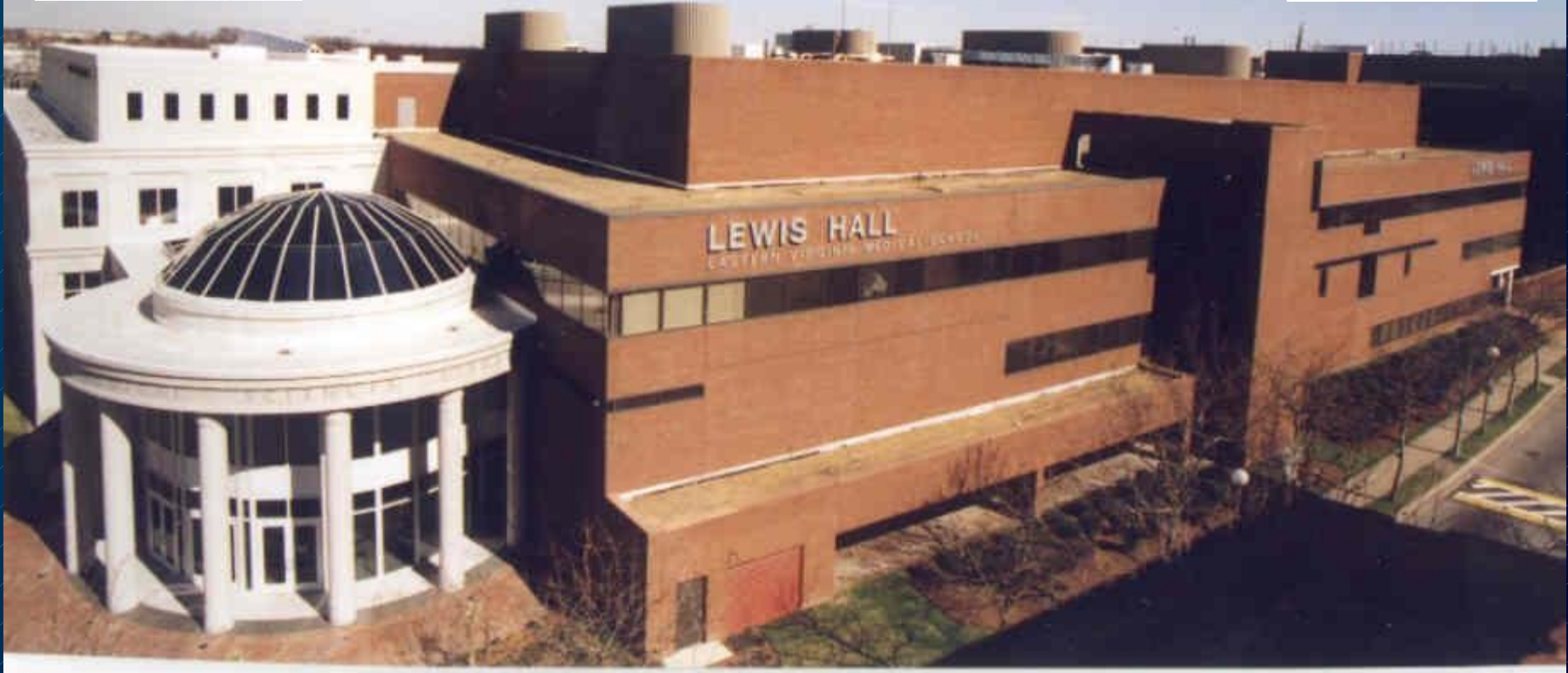




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Norfolk, Virginia



Biochemical (PSA) Relapse / Failure

| | |
|------------------------------------------|------------|
| New prostate cancer cases per year (07) | ≈ 220,000 |
| 75% have treatment for localized disease | 170,000 |
| 25-35% experience PSA-only recurrence | ≈50-60,000 |

Men are younger and healthier at time of PSA-only recurrence

Required: Precise Definition of PSA Recurrence

- ▶ Surgery: <0.07 , <0.1 , <0.2 , <0.3 , <0.4 , <0.5
(with one or more confirmatory levels)
Prostate Guidelines Study - 2005
- ▶ EBRT: ASTRO / Absolute Nadir / Nadir + “#”
(time to nadir, bounce, consecutive rises)
RTOG Consensus Conf – 2005
Nadir +2

Characteristics of Rising PSA Cohort

- ▶ Healthy, excellent performance states immunocompetent
- ▶ Limited (microscopic/sub clinical) disease burden
- ▶ Marker(s) to assess progression and treatment effect

Healthy Cohort w/Minimal Disease

- an ideal situation for success with “standard” therapy and opportunities for discovery testing novel therapies

But...

- Converting an emotionally and physically well population to an anxious cohort at risk for treatment toxicity without, as yet, well defined benefit

Case Study

Levels of Evidence

- a – >1 RCT of acceptable size
- b – 1 RCT of acceptable size
- Large cohort studies
- Case Control Studies
- Case Series
- Expert Opinion

Case Study

60 year old healthy male, no comorbidities

T1c, Gleason 4+3, PSA = 10, bone scan-neg

RRP with bilateral LND performed (*8 nodes/side*)

Pathology: Gleason 4+4, focal ECE;
margins, SV, and nodes are negative.

Adjuvant Trials Eligibility

- ▶ EBRT
 - ▶ *Extracapsular extension*
 - ▶ *Positive margins or SV*
- ▶ CTX Trial Eligibility (Tax 3501)
 - ▶ *pT₃*
 - ▶ *G 8-10*
 - ▶ *Node positive*

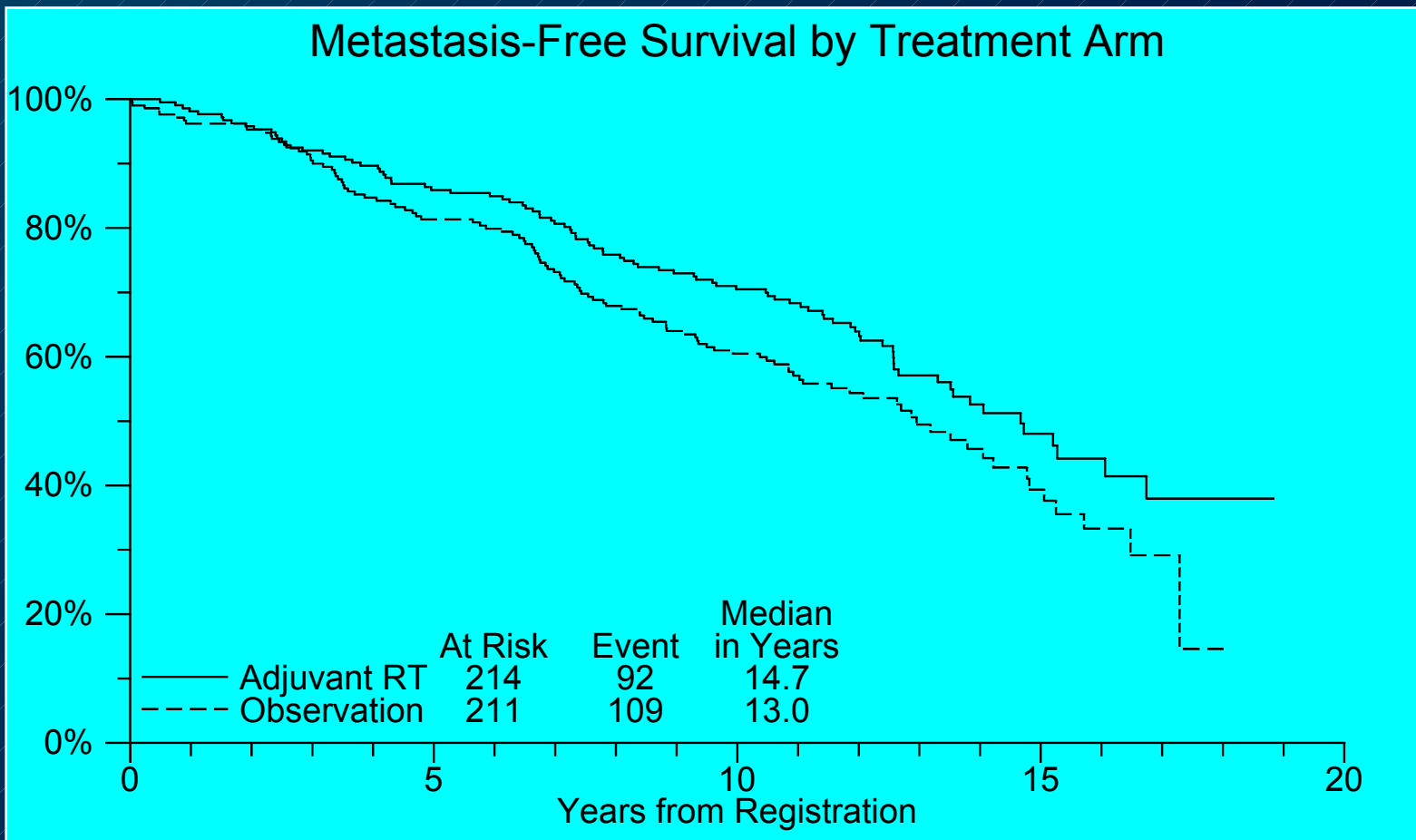
Adjuvant Radiation Therapy Trials (Level 1)

| Group | N eval | Median f/u (yrs) | PFS | OS | met free |
|-------------|--------|------------------|---------------------|----------|----------|
| EORTC 22911 | 1005 | 5.0 | 72 vs 52 p < 0.0001 | NS | |
| SWOG 8794* | 410 | 9.7 | 67 vs 48 p = 0.0001 | p = 0.11 | p = .06 |
| GERMAN | 385 | 3.3 | 81 vs 60 p < 0.0001 | NS | |

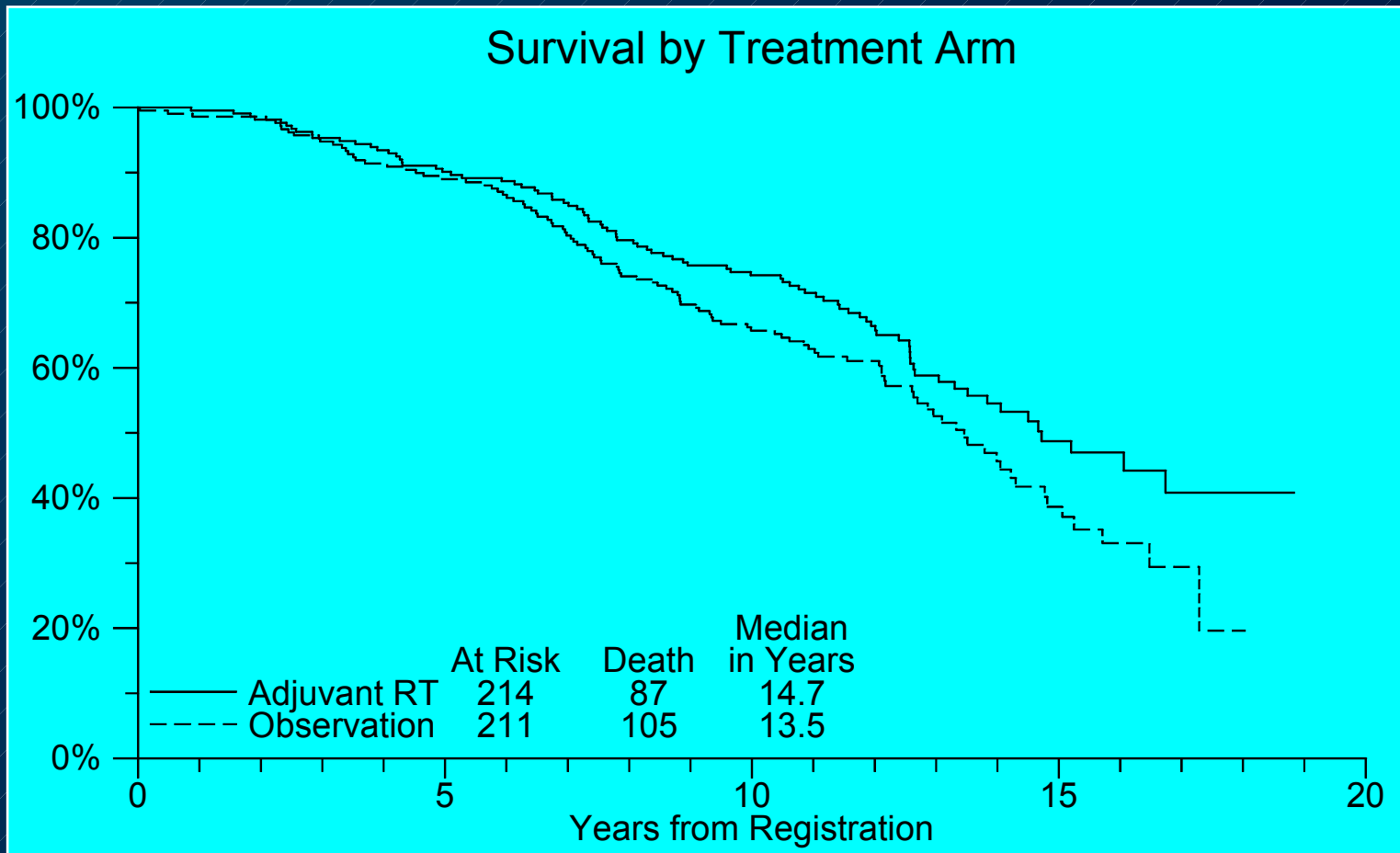
RT: 60 – 64 Gy for pT3a or pT3b or + margins

*proctitis and stricture > in EBRT arm

Adjuvant radiation significantly improved metastasis free survival ($p=0.031$; HR 0.74, 95% CI 0.56,0.97), the study's primary endpoint.



Overall survival was improved with radiation
($p=0.046$; HR 0.75, 95% CI 0.56, 1.00).



Adjuvant RCT Trial Outcomes

- ▶ 3 Trials - Level I A
 - ▶ *CaPSURE database (Urol: 70, 106, 2007)*
 - ▶ *1.8% of 5336 men had adj EBRT*

PSA Profile After R.P.

@ 3 months after R.P. = <0.1

@ 6 months after R.P. = <0.1

@ 12 months after R.P. = <0.1

@ 15 months after R.P. = 0.25

@ 18 months after R.P. = 0.4

@ 21 months after R.P. = 0.8

Bone and CT scan – negative

PSA DT = 3 months

Critical Questions

- ▶ Is the rising PSA after local therapy secondary to:
 - ▶ *Persistent local disease*
 - ▶ *Distant metastasis* *or*
 - ▶ *Both*

-
- Does a Rising PSA warrant:
 - Local therapy only?
 - *EBRT*
 - Systemic therapy only?
 - *Androgen Deprivation – Chemotherapy*
 - **Combination?**

Needle Bx of UV Anastomosis

J Urol 144:921, 1990

- ▶ 57 pts with PSA > 0.4 (6-240 mos post RP)
 - ▶ *Neg CT / bone scan / cystoscopy*
 - ▶ *42% positive needle bx*
 - ▶ *DRE not helpful*

- ▶ *53% of PSA to undetectable after EBRT*

Needle Bx of UV Anastomosis

J Urol 155: 111, 2001

- ▶ 33 pts w/ positive post RP bx
- ▶ 34 pts w/ PSA failure only
- ▶ 3 yr PSA <0.2 Not stat different 39% - 49%

R.P. vs WW in Early CaP

NEJM 352, (19), 1977, 05

- ▶ In RP arm at 10 yr follow up
 - ▶ *Local (clinical) progression 19.2%*
 - ▶ *Distant metastases 14%*

MRI of Skeleton in High Risk Patients

JCO 25: 2281, 2007

- ▶ MRI detected metastases
 - ▶ *7 / 23 pts (30%) with negative bone scan*
 - ▶ *8 / 17 pts (47%) with equivocal bone scan*

Disseminated Tumor Cells (DTC)-Biology

AUA: 657, 2007

- ▶ DTC detected in 75% (395 / 537) pre-R.P.
in 79% (19 / 24) with PSA failure
in 56% (58 / 103) NED
- ▶ Tumor cell dormancy as an intermediary
between 1^o + metastasis

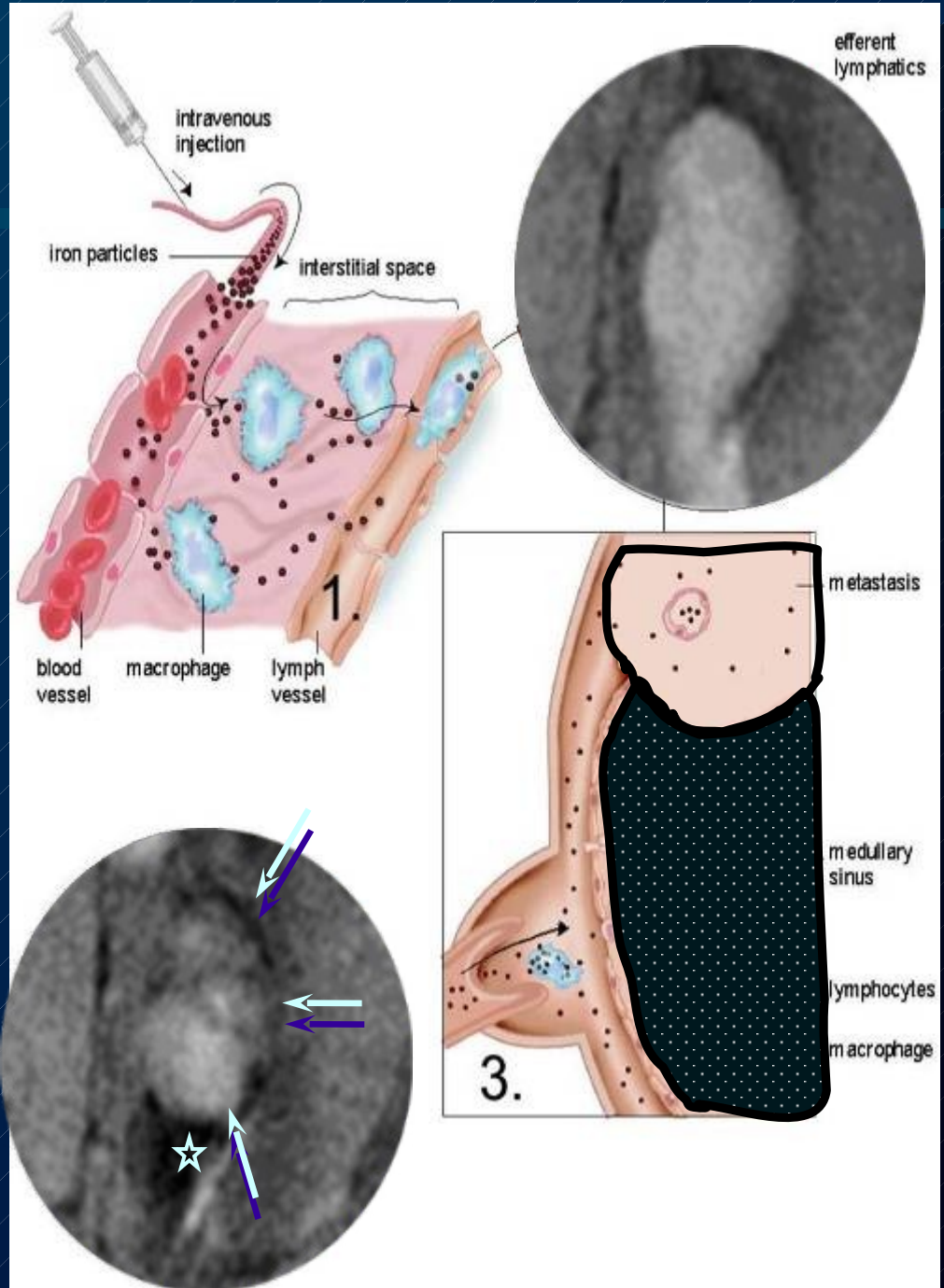
Nanoparticles

Ferumoxtran-10

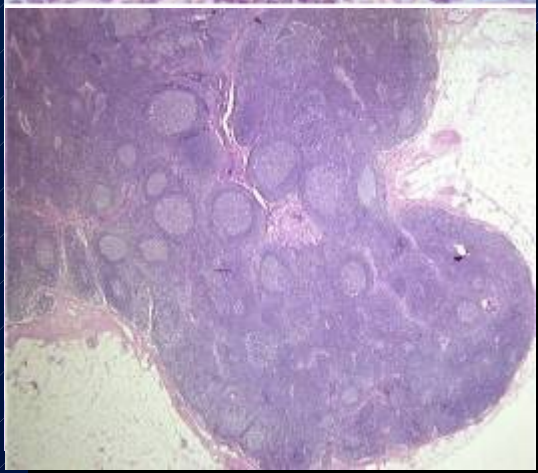
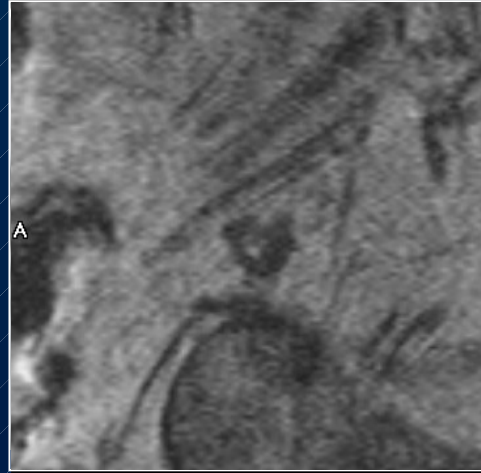
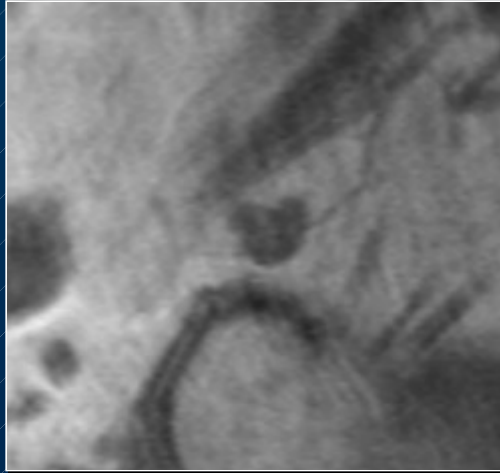
(Combidex / Sinerem)

MR Lymphography

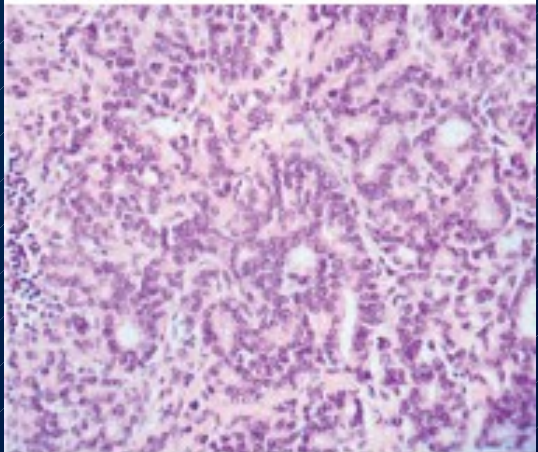
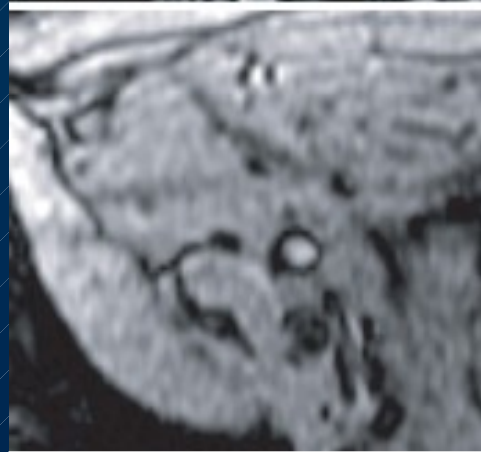
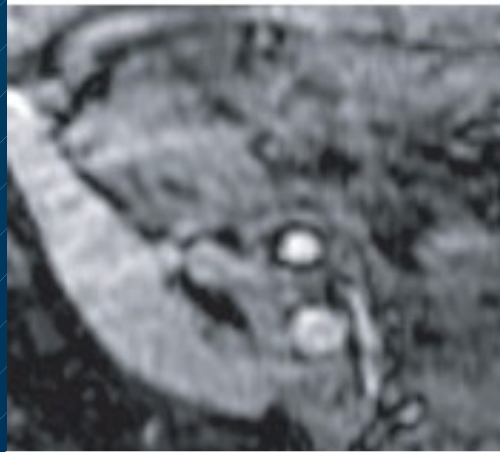
MRI



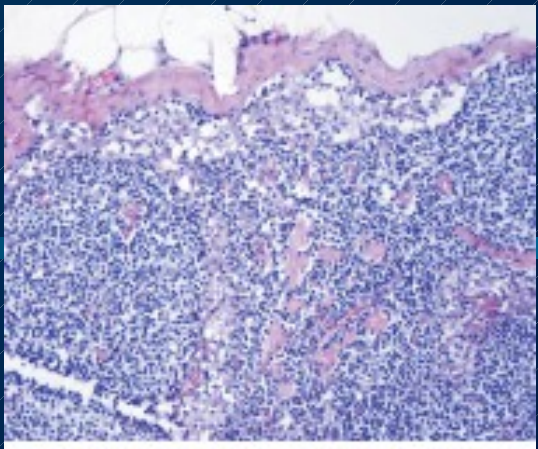
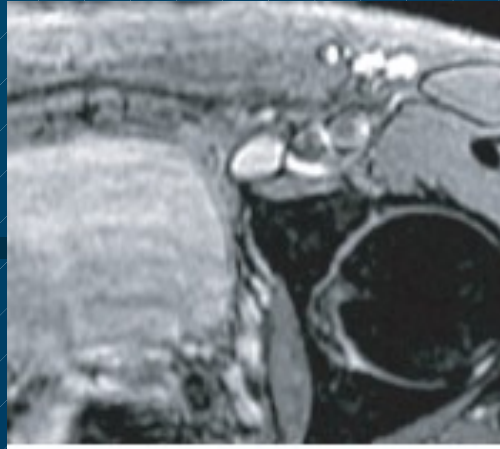
Micro



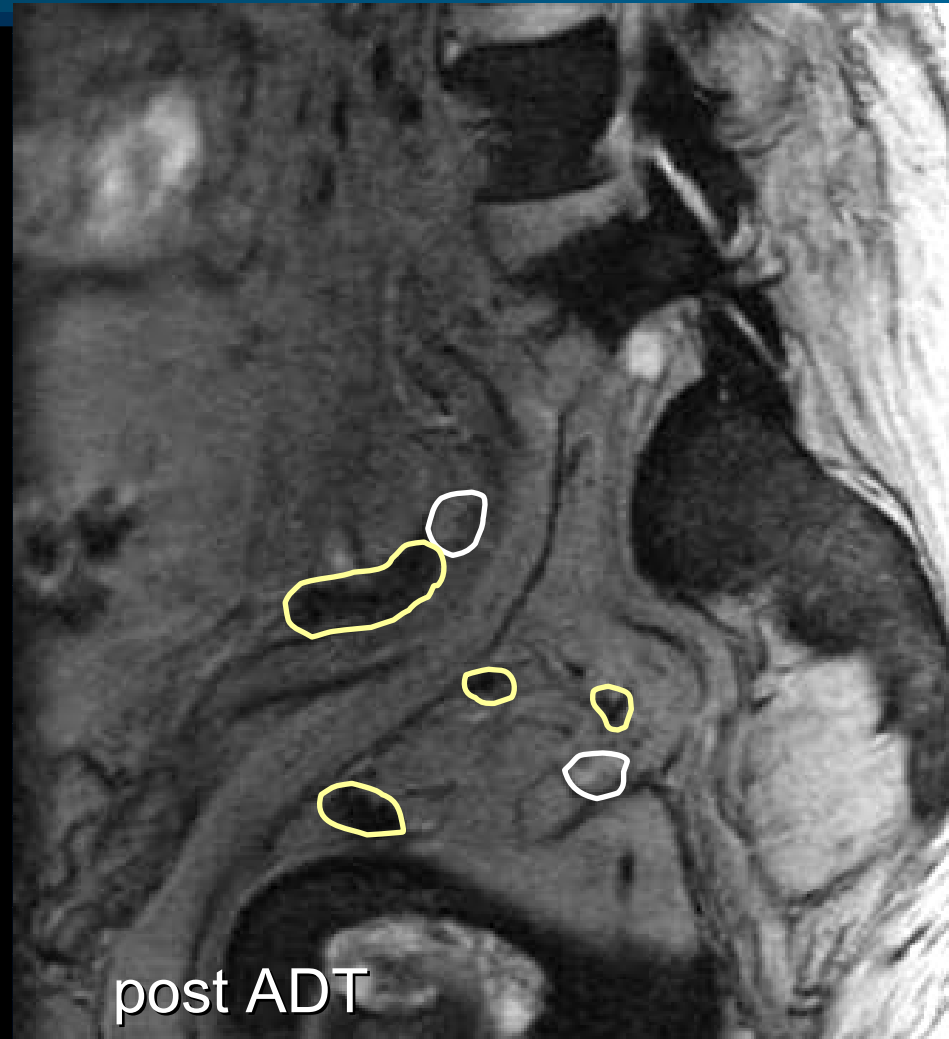
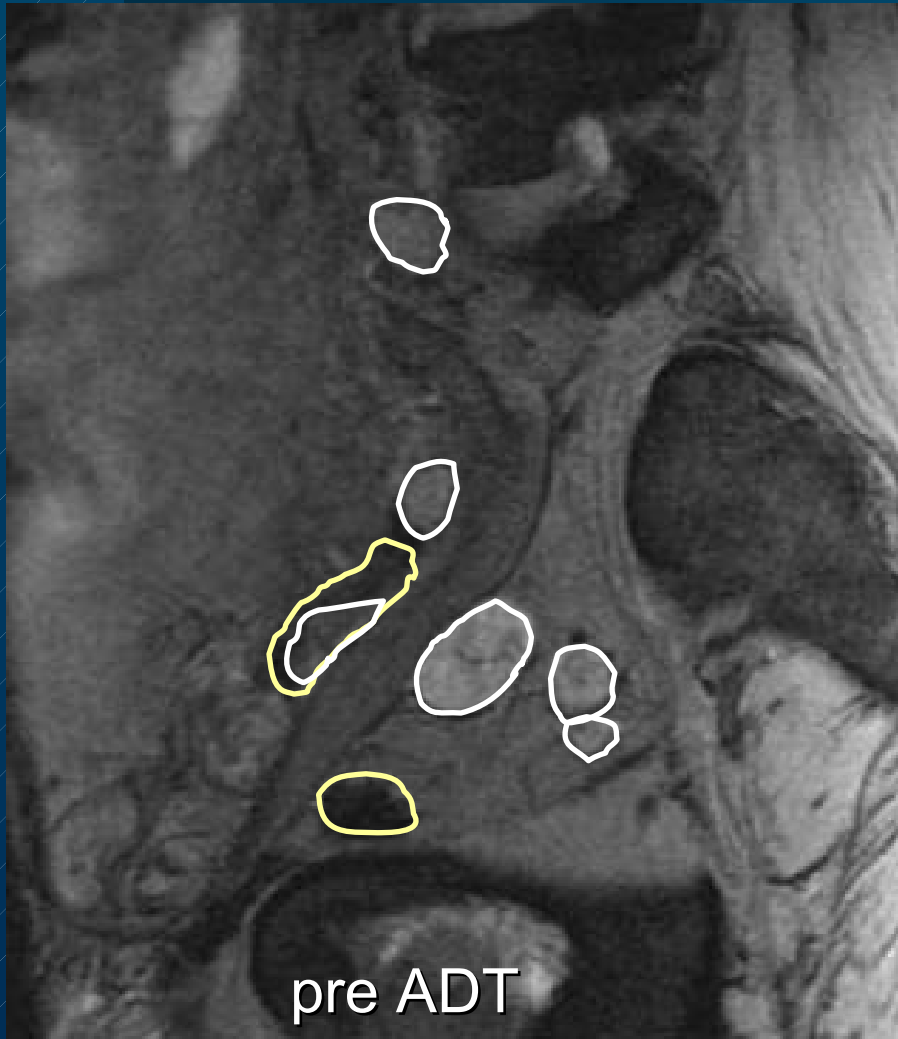
Macro



Benign



Partial response to ADT



Introduction

localization

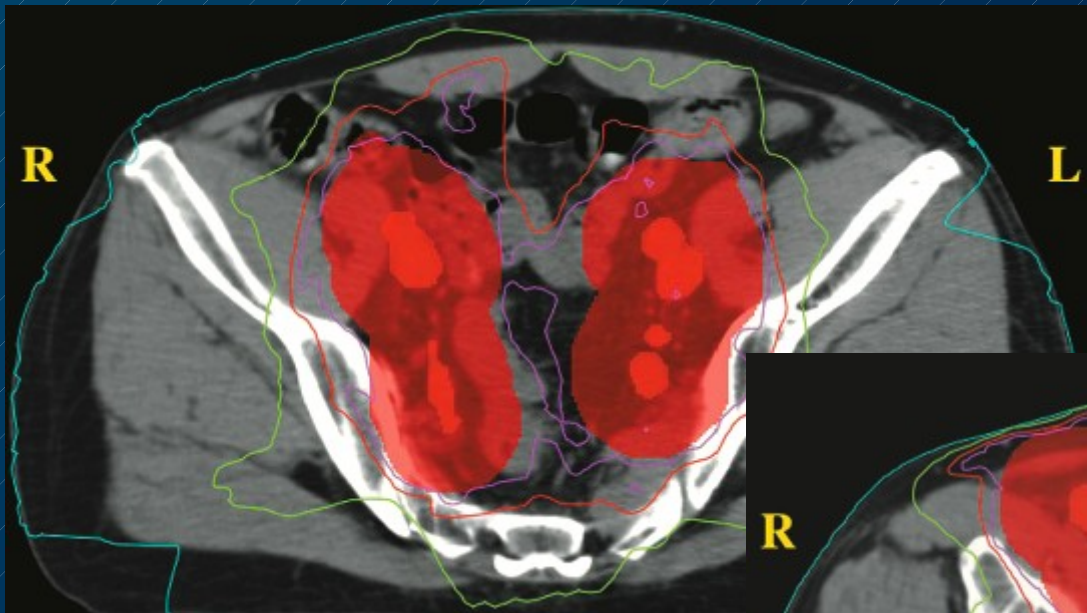
Local Staging

Nodes

Recurrence/FU

New Developments

IMRT planning

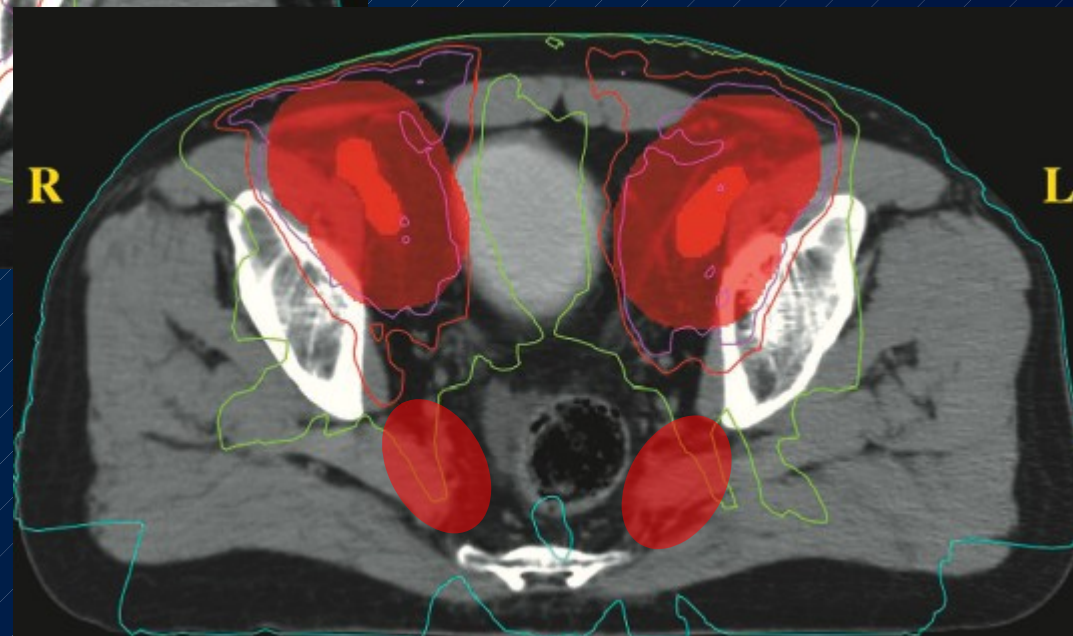


45Gy

40Gy

30Gy

10Gy



Introduction

localization

Local Staging

Nodes

Recurrence/FU

New Developments

Findings That Favor Local Failure

- ▶ PSA rise ≥ 3 yrs after R.P.
- ▶ Slow (>12) mos PSA DT
- ▶ Favorable grade 3+3, 3+4
- ▶ CAVEAT –
 - ▶ *Long period of dormancy which masks eventual DF for many years*

Estimated Risk of Death @ 10 yrs after RP

JAMA 294:433, 2005

| PSA DT | PSA Recurrence >3 yrs after RP | | PSA Recurrence ≤ 3 yrs after RP | |
|---------------|--------------------------------|-----|---------------------------------|-----|
| | < 8 | ≥ 8 | < 8 | ≥ 8 |
| ≥ 15 mo | 2% | 4% | 7% | 14% |
| 9.0 – 14.9 mo | 5% | 4% | 15% | 31% |
| 3.0 – 8.9 mo | 16% | 32% | 45% | 74% |
| < 3.0 mo | 41% | 70% | 85% | 99% |

Predicting Outcomes of Salvage EBRT (level 4)

JCO 25: 20035, 2007

- 1,540 patients from 17 centers (1987-2005)
- ▶ Outcome measure = PSA > 0.2 (confirmed)
- ▶ Overall 6 yr PSA free = 32% (CI 28-35%)
- ▶ PSA sensitive
 - ▶ < 0.5 = 48%
 - ▶ 0.5-1.0 = 40%
 - ▶ 1.0-1.5 = 28%
 - ▶ >1.5 = 18%
- ▶ PSA < 0.5, PSADT <10 mos, Gleason 8-10 = 41%

Salvage EBRT Improves Survival

ASCO Feb, 2008

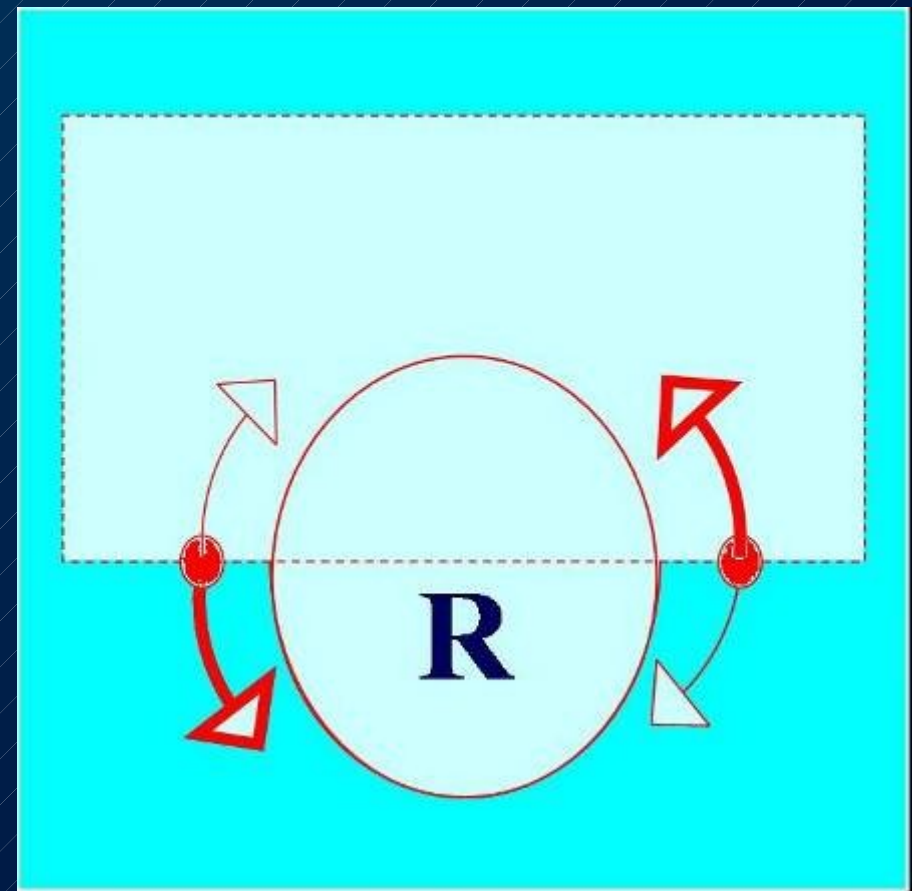
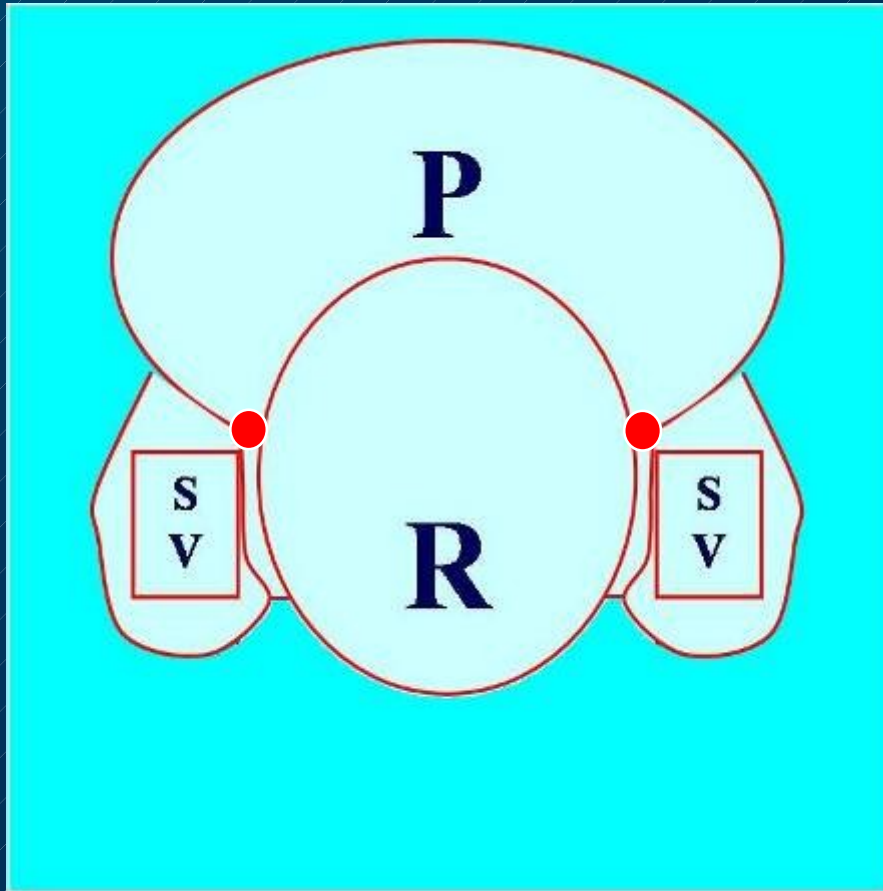
- ▶ 10 yr survival
 - ▶ 82% *with salvage EBRT*
 - ▶ 62% *without salvage EBRT*
- * Best results with short PSADT
- * J Hopkins study

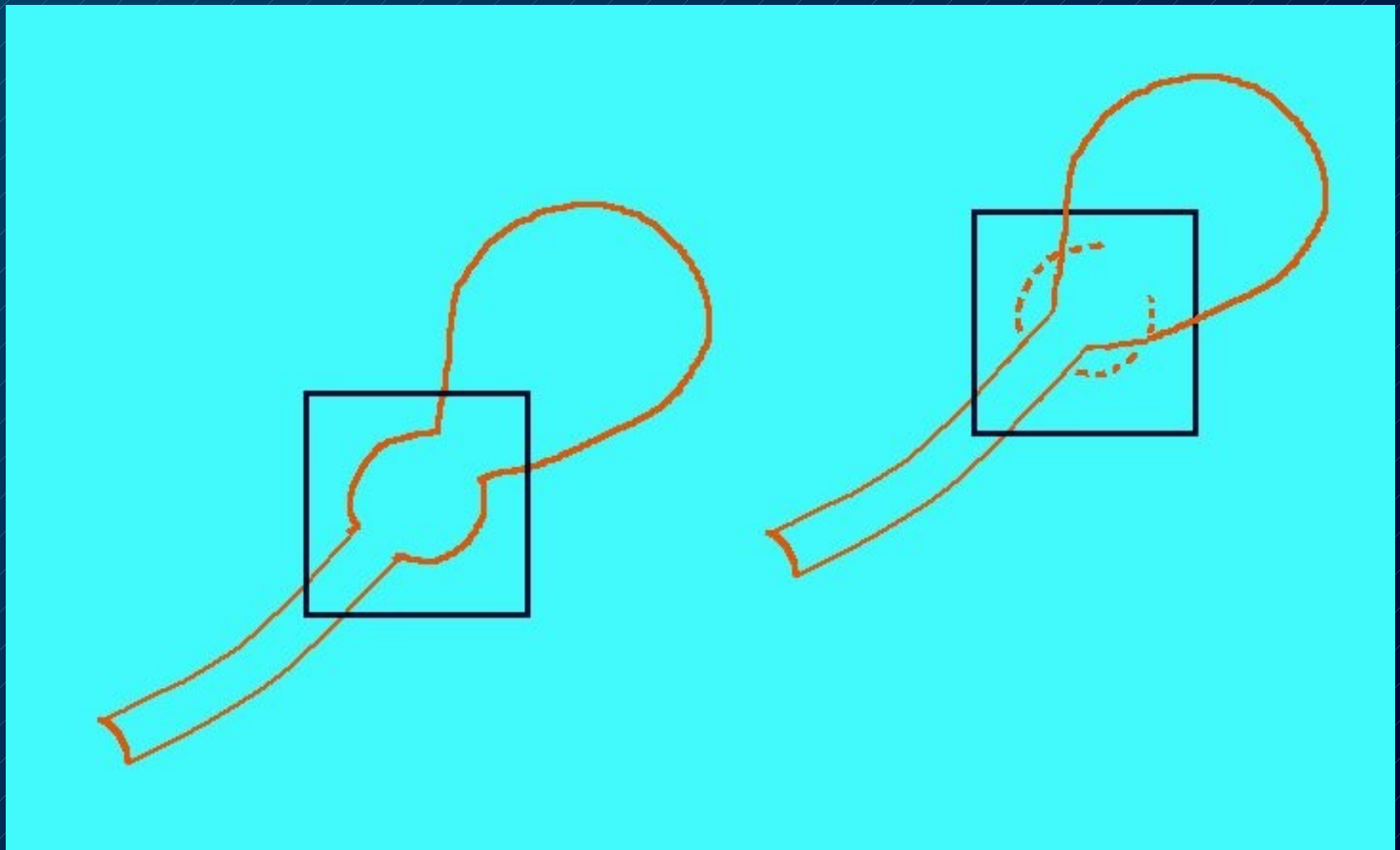
Nomogram For Our Patient

- ▶ 40% probability of progression-free @ 6 yrs
- ▶ 75 pts for PSA DT
- ▶ 45 pts for Gleason 8
- ▶ 25 pts for PSA pre-RP (9)
- ▶ 25 pts for PSA pre-salvage (0.8)

-
- ▶ Failure after external beam (primary or salvage) occurs for 3 reasons
 - ▶ *Cancer within the pelvis but outside the field (expand field)*
 - ▶ *Distant micrometastases (systemic therapy)*
 - ▶ *Radioresistant tumor within the field (dose/sensitizing agents/hyperthermia)*

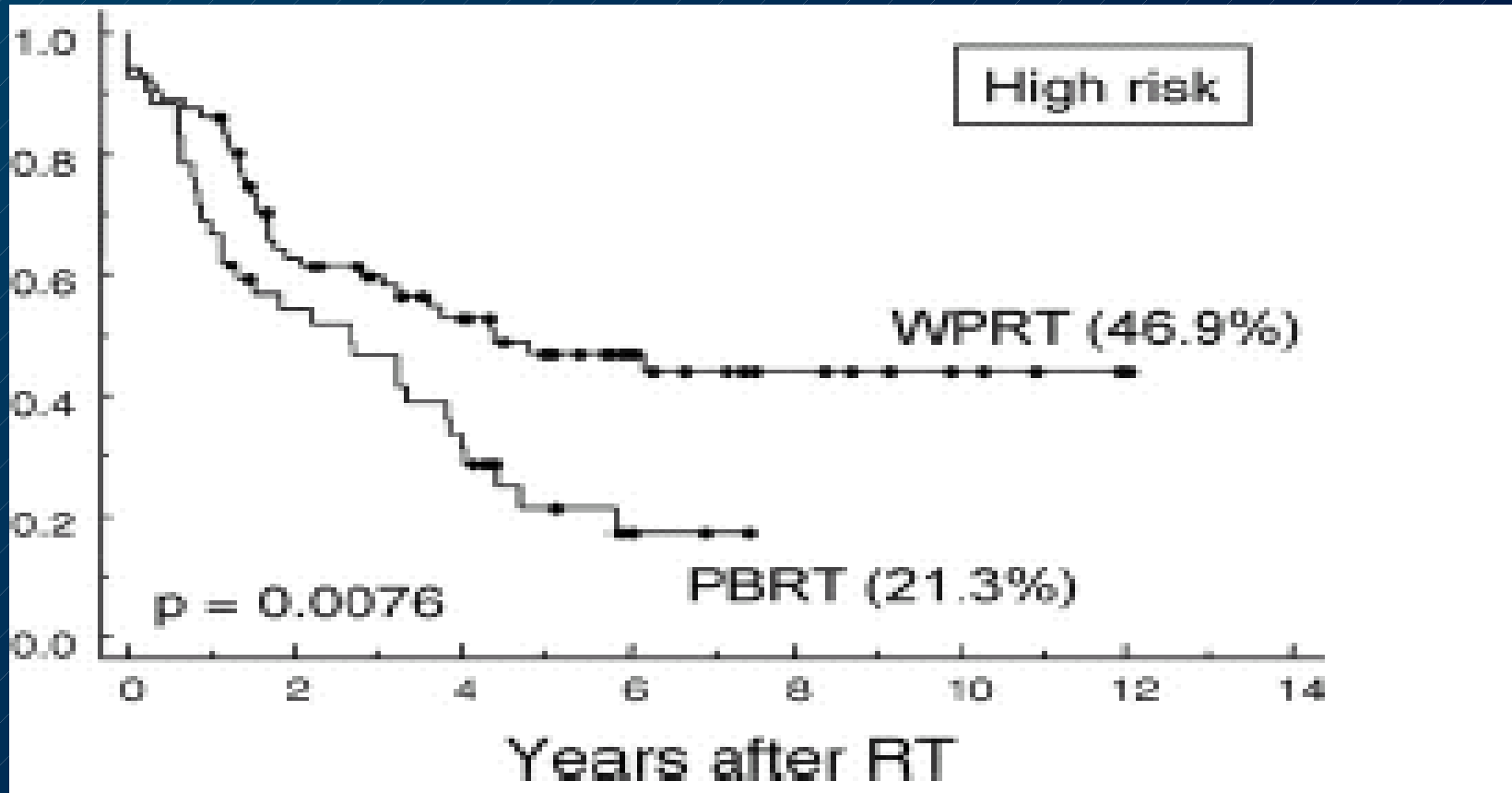
Salvage Radiation





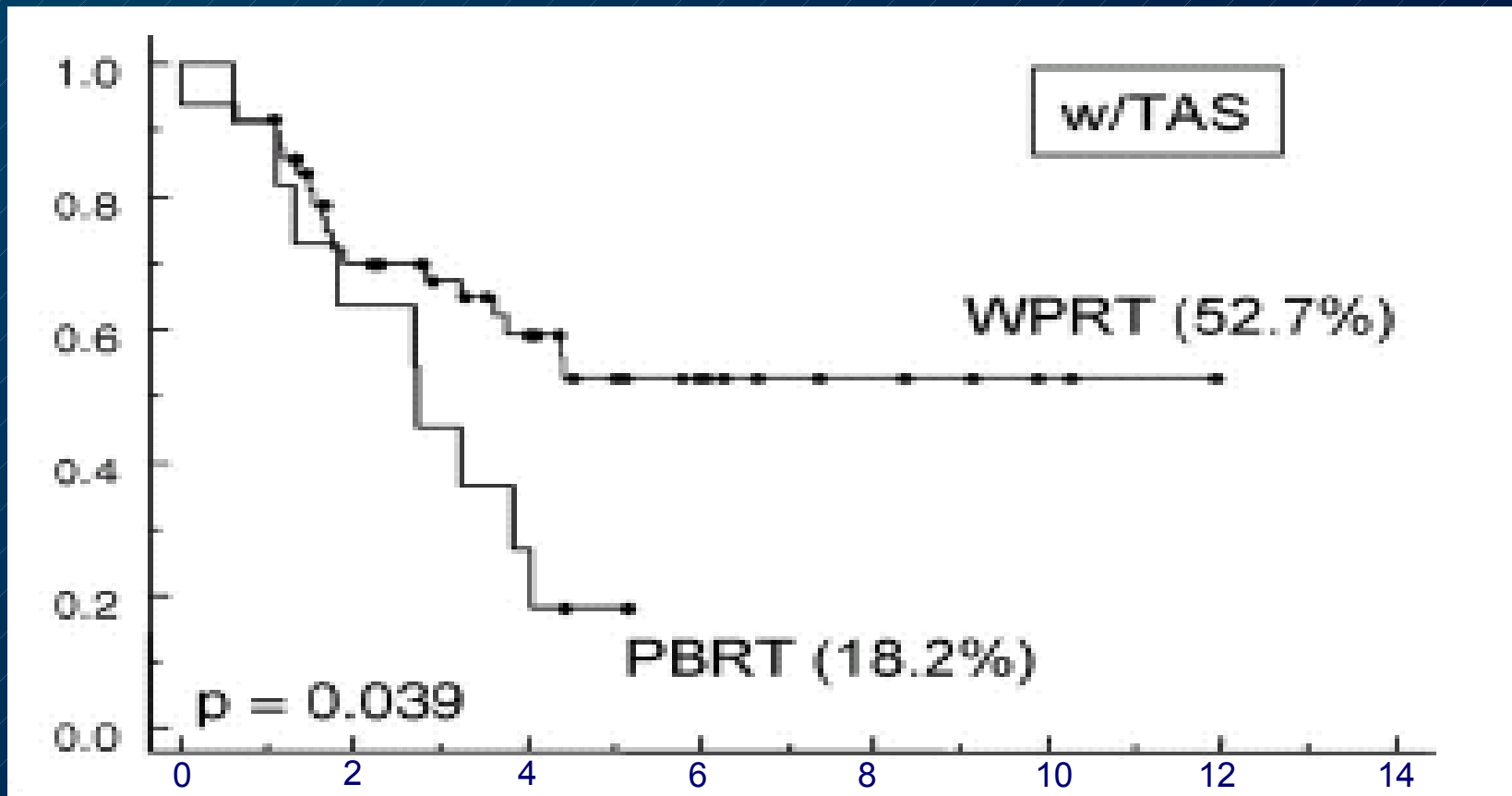
Biochemical Relapse-Free Survival

Int J Rad Onc, In Press



Biochemical Relapse-Free Survival

Int J Rad Onc, In Press



Years after RT

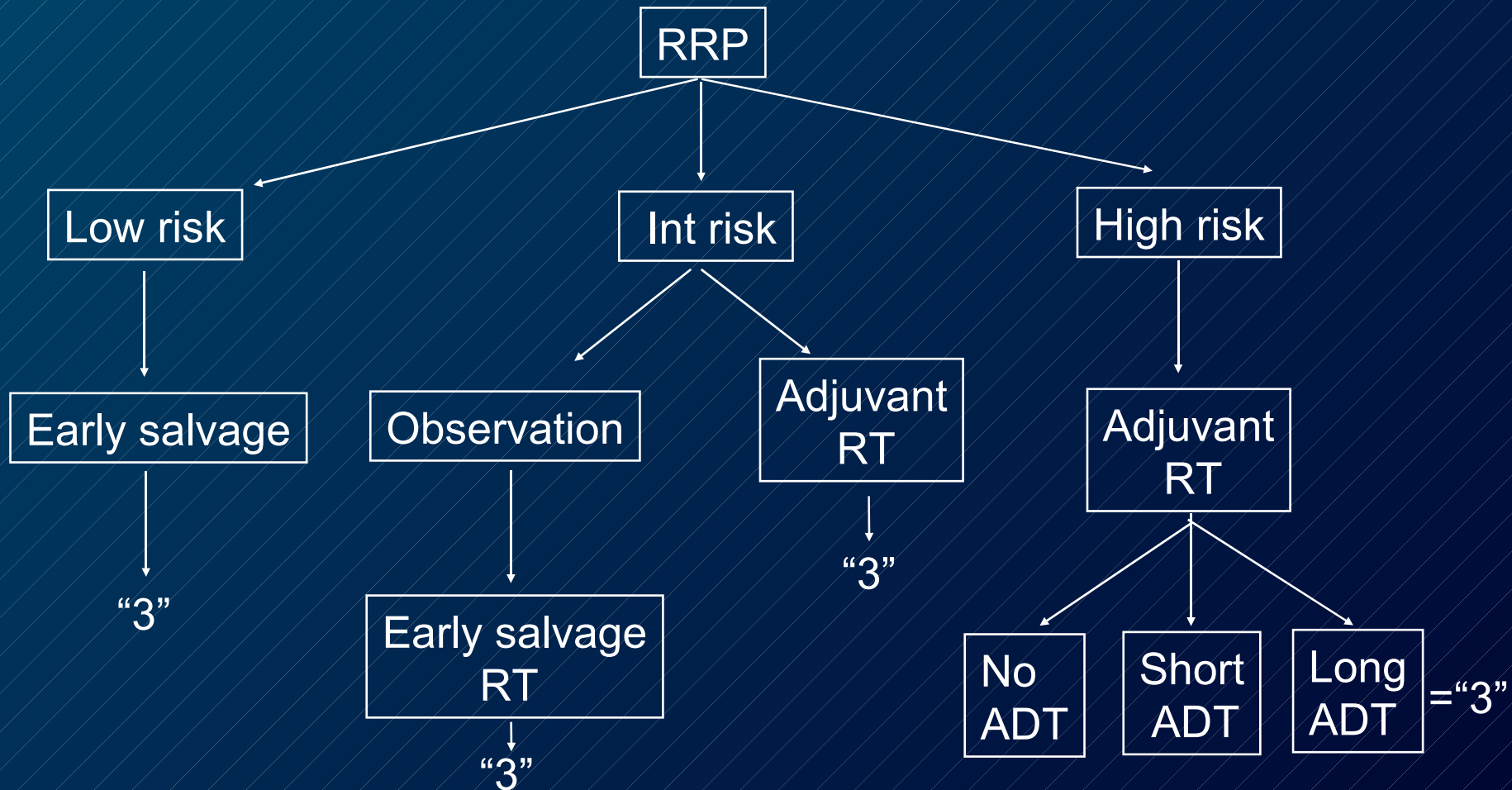
A Phase III Salvage Trial of Short Term AD w/ Pelvic Lymph Node or Prostate Bed Only RT SUPPORT (Level 1)

- Arm I : PBRT Alone
 - *PBRT (64 – 70.2 Gy)*
- Arm II: PBRT + STAD
- Arm III: PLNRT + PBRT + STAD
 - *STAD for 4-6 mo, beginning 2 mo before RT*

1,700 pts

UK – NCIC RADICALS trial

Adj vs Salvage – No AD vs L/S AD- Level 1



Opened: Jan 2007

Endpoint = CSS & OS

Target – 4000 pts

Early = 2 rises > 0.1 or any 3 rises

Salvage EBRT for Rising PSA

RTOG 0622 – Phase II

- ▶ PSA > 2.0
- ▶ Samarium 153 followed in six weeks by:
 - ▶ *Int Risk - EBRT ± AD*
 - ▶ *High Risk - EBRT ± AD ± pelvic field*

RCT For Rising PSA - Closed

| | Trial | Accrual to Date/ Anticipated Accrual |
|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| RTOG 0014 | Patients with High Risk, Hormone - Naïve Prostate Cancer: A.D. with 4 Cycles of Immediate Chemotherapy vs A.D. Blockade with Delayed Chemotherapy | 17 / 1,050 |

Androgen Deprivation

- ▶ Significant decrease in BMD
- ▶ Significant increase in fracture
(M_0 – non path)
- ▶ Changes body composition
muscle – fat
- ▶ Metabolic Syndrome – lipid profiles;
cardiovascular risk

Osteoporosis Rx with A.D. (RCT) (Level 1)

- ▶ Pamidronate
(60 mgs q 3 mos) Maintains BMD
- ▶ Zoledronic acid
(4 mgm q yr) Restores BMD
- ▶ Alendronate
(70 mgm q wk) Restores BMD

Trials For Rising PSA After EBRT or RP

- ▶ Vaccinia / fowl pox / TRI Com - ECOG 9802
- ▶ Lapatinib Trial EFG TK1 - ECOG 5803
- ▶ Revlimid

Androgen Deprivation & Immunology

- ▶ T + DHT increase TF – beta
 - ▶ *Negative immune response modulation*
- ▶ Thymus involutes during adolescence
 - ▶ *Castration restores thymus in rats*
 - ▶ *Dose dependant inhibition by T*
- ▶ Androgen deprivation - ↑ T cells # + function

-
- ▶ Today's Research
(Basic and Clinical)
 - ▶ Tomorrow's Practice