



University of California  
San Francisco

*advancing health worldwide™*

Mack Roach III, MD  
Professor Radiation  
Oncology and Urology,  
*UCSF*

## **Comparing Salvage SBRT with Other Salvage Modalities (e.g., Surgery, HIFU, Cryotherapy, LDR, HDR)**

# Disclosures:

- **Full-time faculty from UCSF**
- **Consulted for almost every drug company providing drugs for treating prostate cancer**
- **Served on Advisory Board for Accuray**
- **Up-to Date Prostate Cancer**
- **NCCN Prostate Guidelines**
- **No other relevant disclosures**

# Why Discuss this topic?

1. ~15 to 75% of CaP pts recur after definitive RT
2. Recurrences – local? +/- regional? +/- distant?
  - a) Local salvage therapies?
  - b) Regional salvage therapies?
  - c) Local & regional salvage
  - d) Suitable for following carefully?
  - e) Not suitable for more radiotherapy
3. **FOCUS on Prostatic recurrences (not oligo mets)**
  - a) Comments on MDT

# **Common Myth by Urologist:**

**“If you have surgery, you can have  
radiation afterwards,  
but if you have radiation first ...”**

## Types of Salvage Therapy after EBRT *CaPASURE (n=430)*

**Androgen Deprivation Therapy 93.5%**

**Cryotherapy 3.0%**

**EBRT 1.9%**

**Radical Prostatectomy 0.9%**

**Unknown 0.5%**

**Brachytherapy 0.2%**

**Agarwal et al. Cancer 2008; 112:307-14**

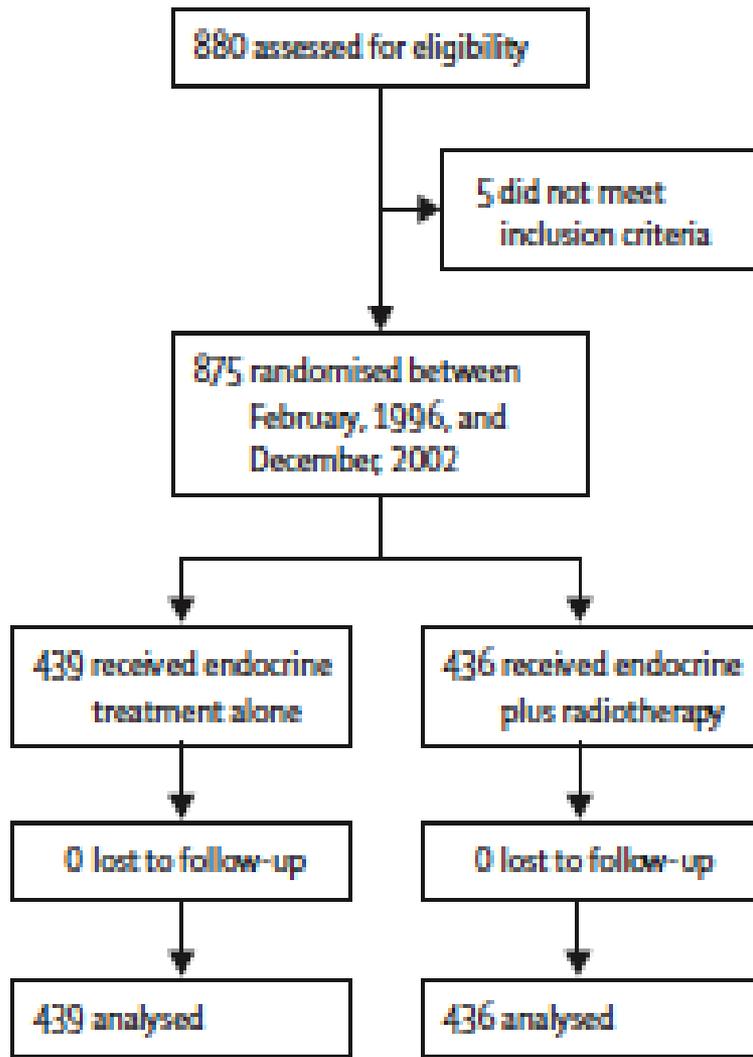


Figure 1: Trial profile

# Widmark et al Lancet 2009

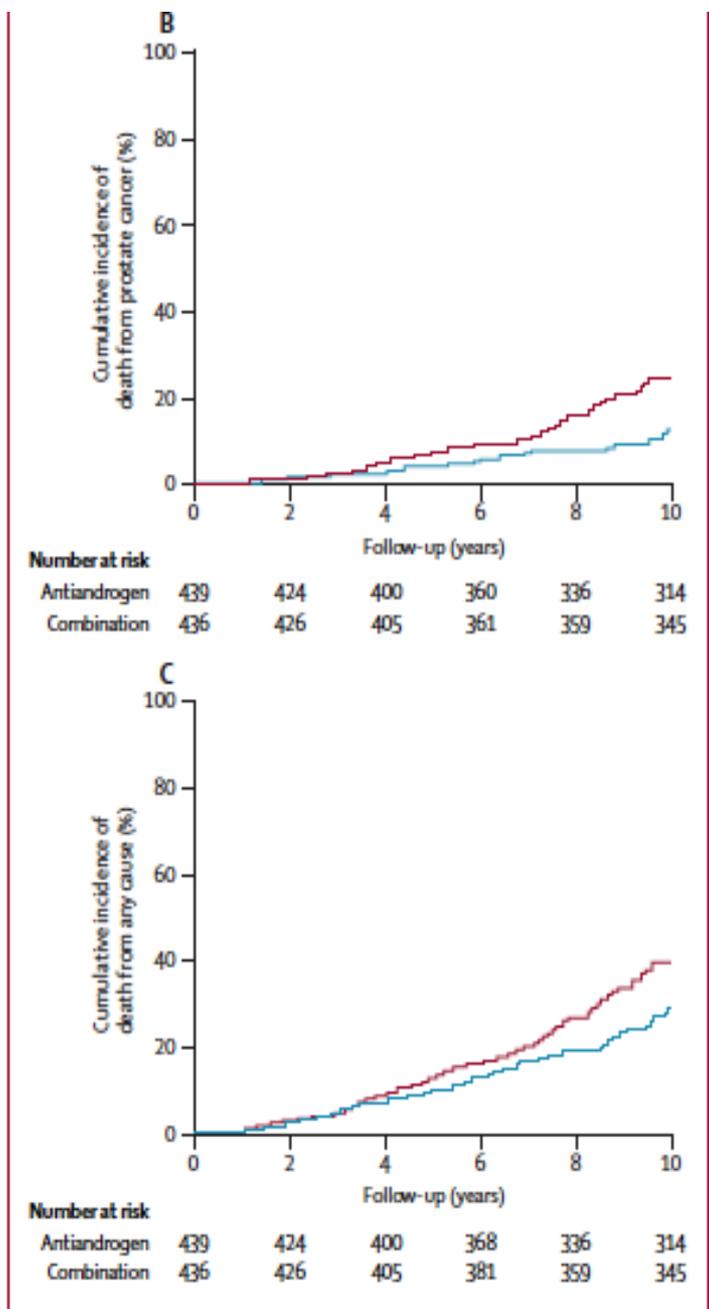


Figure 2: Cumulative incidence of (A) PSA recurrence, (B) death from prostate cancer, and (C) death from any cause

## A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER).

Valle et al. Eur Urol 80:280-292, 2021

Modality	Age (yr)	PSA (ng/mL)	Peri ADT use (%)	Median follow-up	Number of Studies (n)	Number of patients (n)
RP	65	6.0	16	47	52	2686
Cryosurgery	66	5.8	35	32	32	5153
HIFU	69	5.0	18	33	20	1783
SBRT	72	4.0	37	26	8	261
HDR	71	4.5	43	40	16	586
LDR	69	5.5	37	52	32	853
Totals:	-	-	-	-	160	11,322

**n=56**

Modified

Comparing Salvage SBRT with Other Salvage Modalities (e.g., Surgery, HIFU, Cryotherapy, LDR, HDR)

**Table 3**

**Covariate-adjusted meta regression comparing efficacy and toxicity between salvage modalities and prostatectomy (modified)**

	5-yr RFS	Severe GU Toxicity	Severe GI toxicity
<b>Radical prostatectomy</b>	53% (46-59%) OR 1.0 (Ref.)	21% (16-26%)	1.5% (0.4-3.2%)
<b>Cryotherapy</b>	57% OR 1.2	15%	0.9%
<b>HIFU</b>	46% OR 0.76	23%	0.8%
<b>SBRT</b>	56% OR 1.13	5.6% ( <i>p</i> <0.001)	0.0% ( <i>p</i> =0.07)
<b>HDR</b>	58% OR 1.25	9.6% ( <i>p</i> =0.002)	0.0% ( <i>p</i> =0.03)
<b>LDR</b>	53% OR 1.02	9.1% ( <i>p</i> =0.001)	2.1

**A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER) Valle et al. Eur Urol. 2021; 80: 280–292.**

**Comparing Salvage SBRT with Other Salvage Modalities (e.g., Surgery, HIFU, Cryotherapy, LDR, HDR)**

## Functional outcomes and complications following salvage radical prostatectomy for post radiotherapy recurrent prostate cancer A meta-analysis

Yachun Zhou, BSN<sup>a</sup>, Xiujun He, BSN<sup>b</sup>, Qin Yu, BSN<sup>c</sup>, Qing Zhong, BSN<sup>c,\*</sup> 

**“Conclusion:** For radio-recurrent prostate cancer, salvage surgery should be performed with caution and only under strict indications due to the relatively high incidence of adverse events. Robotic surgery and shorter operative times are associated with a lower incidence of moderate to severe urinary incontinence, while longer operative times are linked to an increased risk of severe complications.”

Comparing  
Salvage SBRT  
with Other  
Salvage  
Modalities  
(e.g., Surgery,  
HIFU,  
Cryotherapy,  
LDR, HDR)



## Salvage high-intensity focused ultrasound versus salvage radical prostatectomy for radiation-recurrent prostate cancer: a comparative study of oncological, functional, and toxicity outcomes

Brecht Devos<sup>1</sup> · Walid Al Hajj Obeid<sup>2,3</sup> · Colin Andrienne<sup>3</sup> · Romain Diamand<sup>3</sup> · Alexandre Peltier<sup>3</sup> · Wouter Everaerts<sup>4</sup> · Hein Van Poppel<sup>4</sup> · Roland Van Velthoven<sup>3</sup> · Steven Joniau<sup>4</sup> 

**“Conclusion S-HIFU and S-RP could both be considered valuable LST options for patients with radiation-recurrent nonmetastatic PCa with sufficient life expectancy. S-RP is associated with more pad-dependent patients at 12 months.”**

**Salvage high-intensity focused ultrasound (HIFU) for locally recurrent prostate cancer after failed radiation therapy: Multi-institutional analysis of 418 patients. Crouzel et al. BJUI 2017; 119:896-906**

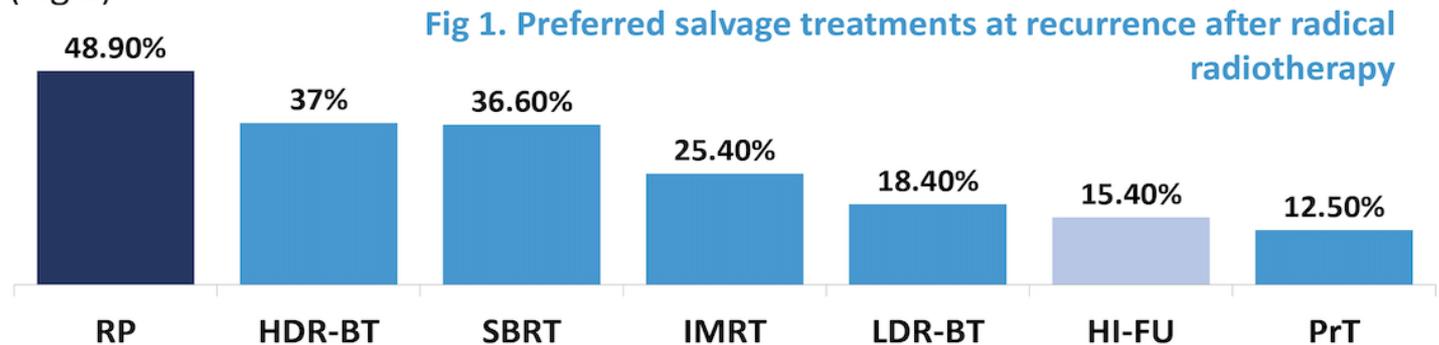
**“Conclusion:**

**S-HIFU for locally recurrent prostate cancer after failed EBRT is associated with 7-year CSS and MFS rates of >80% at a price of significant morbidity. S-HIFU should be initiated early following EBRT failure.”**

## Salvage Treatments for Local Recurrences of Prostate Cancer after Radiotherapy – Results of an International Multi-disciplinary Survey. Monica- Emilia Chirila ... M. Roach III

### RESULTS

- We received 1030 responders from 114 countries. Most of them were either **radiation oncologists** (51.1%) or **urologists** (37.2%) who work in academic centers (56.3%), have more than 20 years' **experience** in treating prostate cancer (56.4%) and at least 10 prostate cancer patients under active treatment/month (53.4%).
- When making the treatment decision, 73.4% of the participants declared that they “Always” or “Usually” present the case in a **tumor board**.
- Almost 83% of the respondents stated **using salvage treatments** in case of a local recurrence after RT.
- ✓ If recommending **salvage treatments**, the following were preferred: radical prostatectomy (RP), HDR-BT, SBRT, IMRT, LDR-BT, HI-FU and proton therapy (PrT) (Fig 1).



*Presented at ASTRO 2021*

## Re-irradiation for local recurrence of prostate cancer – results of an international Survey. Monica- Emilia Chirila ... M. Roach III

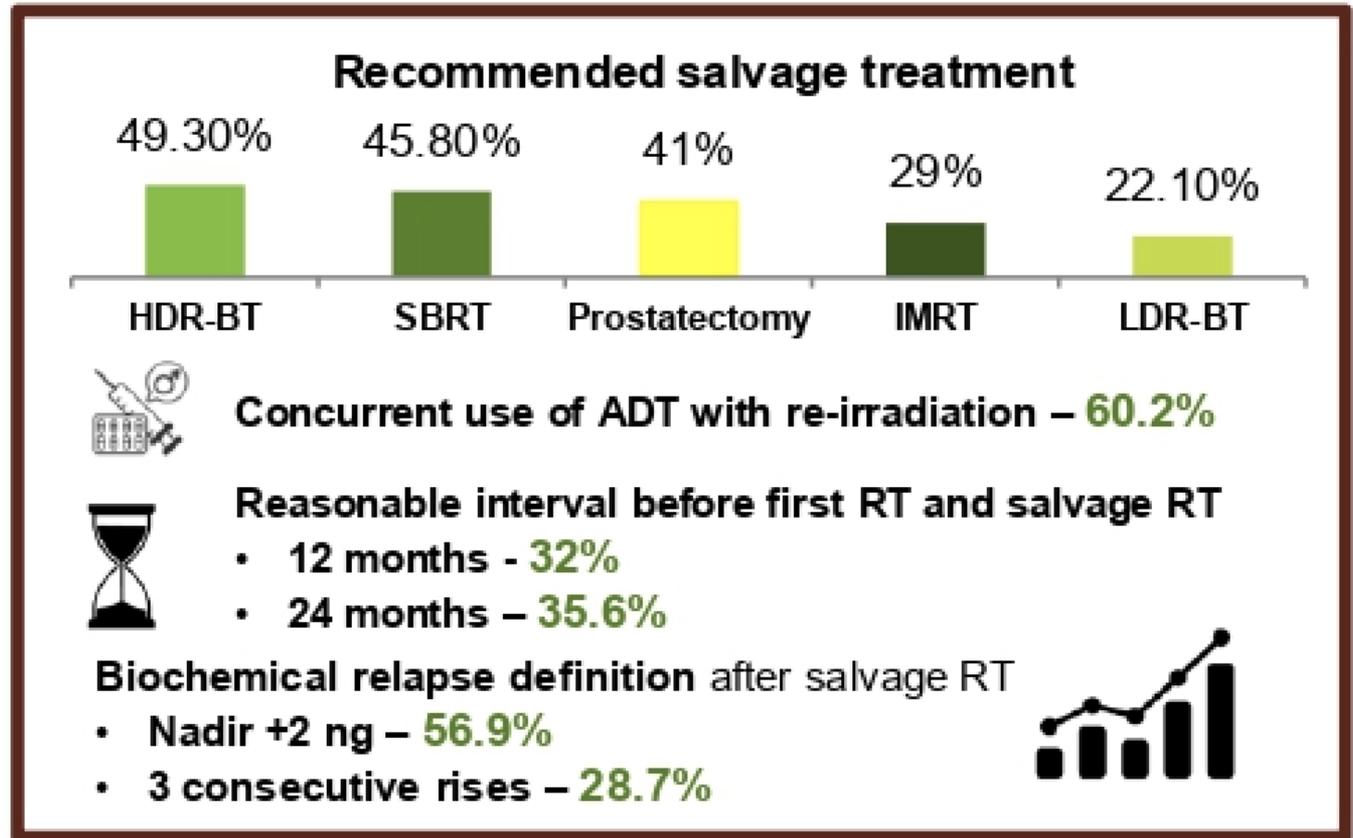


Fig 5. Preference on salvage treatment type, use of hormonal therapy, interval to re-irradiation and biochemical relapse definition after salvage

# Salvage Brachytherapy (Circa 1999)

## Permanent Brachytherapy as Salvage Treatment for Recurrent Prostate Cancer. Beyer Urol 54: 880-883, 1999

- 17 pts 1989-94: I125 120 Gy, /Pd-103 90 Gy
- DFS = 67% PSA < or = 10 vs 25%
- DFS = 83% if low grade vs 30% high grade
- Incontinence 24%

## Salvage Brachytherapy for Localized Prostate Cancer After Radiotherapy Failure. Grado et al. J Urol 53: 2-10, 1999

- 49 pts : I125 /Pd-103 median fu 64.1 mo.
- 5 Year DFS = 34%, DSS = 79%
- 4% rectal ulcers, 6% incont. & persistent pain
- 2% colostomy

**Treatment outcome and toxicity after salvage 125-I implantation for prostate cancer recurrences after primary 125-I implantation and external beam radiotherapy. Moman et al. Brachytherapy 9: 119-25, 2010**

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**RESULTS: ...The freedom from biochemical failure after 1 & 5 yrs' fu were 51% and 20%, respectively.**

**45% pts died of prostate ca. ... a mean fu of 73 mos.**

**Grade 1, 2, or 3 GU toxicity ... 16%, 39%, and 19%, respectively, in the late phase.**

**Grade 1, 2, or 3 GI toxicity ... 48%, 3%, and 6%, respectively, in the late phase.**

**CONCLUSIONS: Freedom from biochemical failure after salvage 125-I implantation ... is limited, and both GU and GI occur frequently.**

**Treatment outcome and toxicity after salvage 125-I implantation for prostate cancer recurrences after primary 125-I implantation and external beam radiotherapy. Moman et al. Brachytherapy 9: 119-25, 2010**

**RESULTS:**

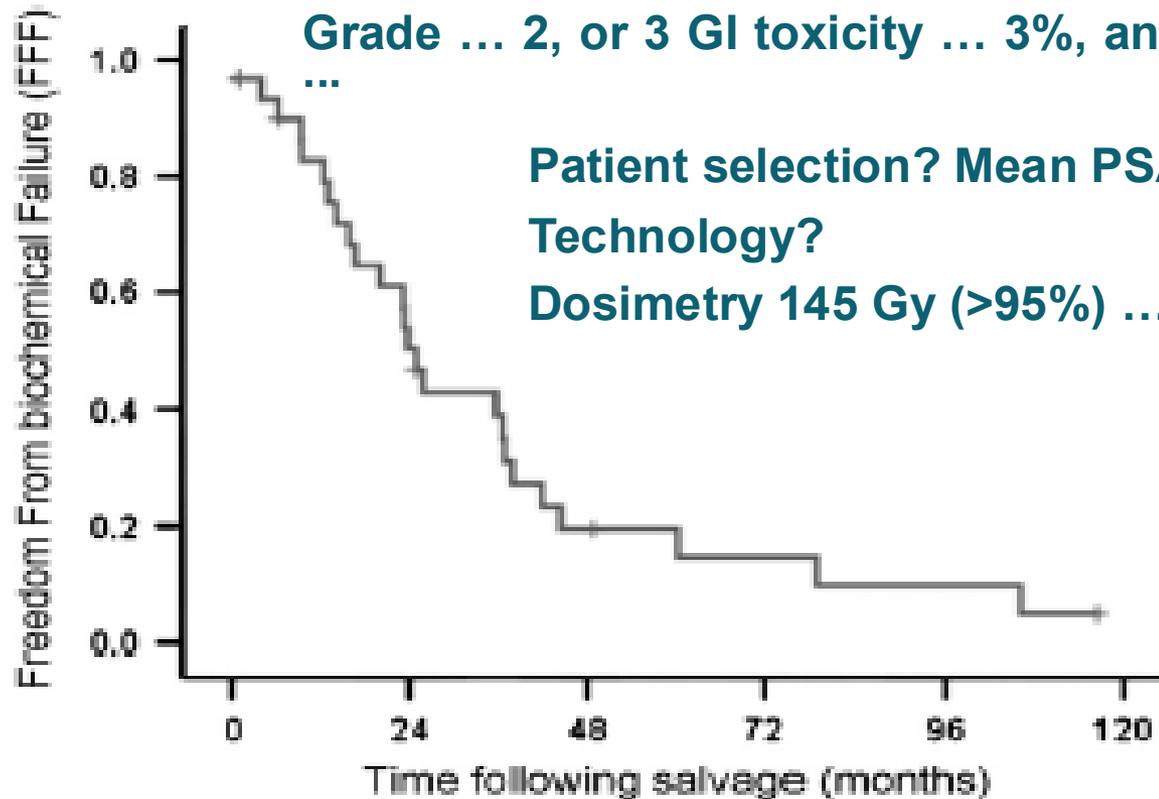
**Grade ... 2, or 3 GU toxicity ... 39%, and 19% ...**

**Grade ... 2, or 3 GI toxicity ... 3%, and 6%, respectively ...**

**Patient selection? Mean PSA=11.4 ng/ml**

**Technology?**

**Dosimetry 145 Gy (>95%) ... urethra  $\leq$ 200%**



**Fig. 3. Kaplan—Meier prediction of freedom from biochemical failure after salvage 125-I implantation.**

**Treatment outcome and toxicity after salvage 125-I implantation for prostate cancer recurrences after primary 125-I implantation and external beam radiotherapy. Moman et al. Brachytherapy 9: 119-25, 2010**

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## **Comments:**

**Patient selection? Mean PSA=11.4 ng/ml**

**Technology?**

**Dosimetry guidelines for PPI: 145 Gy of > 95%, 2/3 & 1/3<sup>rd</sup> 150 & <200% of prescribed dose & urethra  $\leq$ 200% & rectum <100% of prescribed dose**

**Magnetic resonance image-guided salvage brachytherapy after radiation in select men who initially presented with favorable-risk prostate cancer: a prospective phase 2 study**  
Nguyen et al. Cancer 110:1485-92, 2007

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**BACKGROUND:** ... late gastrointestinal (GI) and genitourinary (GU) toxicity and PSA control of MRI-guided brachy used as salvage ...

**METHODS:** ... with rising PSA and +Bx, at least 2 yrs post:

- EBRT (n=13) or brachytherapy (n=12)
- GS  $\leq$ 7, PSA < 10 ng/mL, negative imaging

Phase 1/2 study MRI-guided salvage brachy (*MPD 137 Gy*)

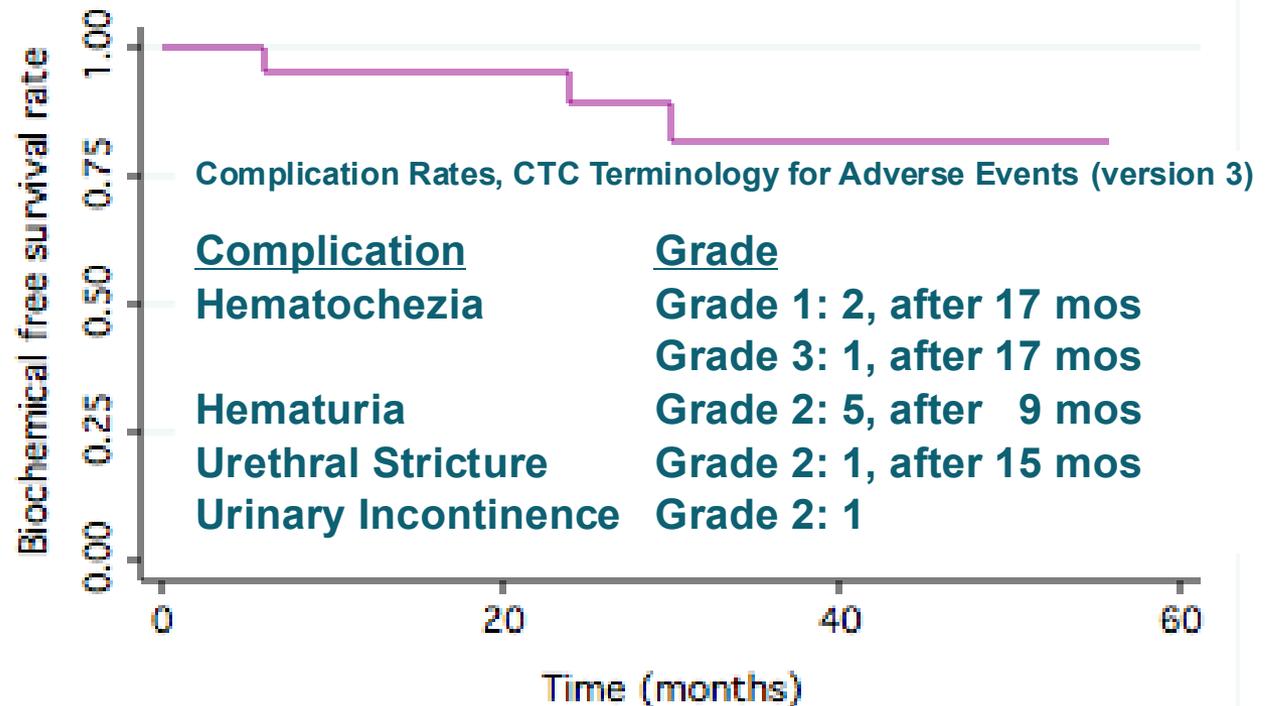
**RESULTS:**

Med fu 47 mos. grade 3 or 4 GI or GU toxicity ~ 30%  
13% required a colostomy and/or urostomy (fistula).  
Interval < 4.5 yrs since RT HR ~ 12 (p= 0.02) grade 3-4  
tox & 25 (p= 0.04) for colostomy urostomy.

## Salvage Permanent Perineal Radioactive Seed Implantation For The Treatment of Localized Prostate Adenocarcinoma Recurrence After External Beam Radiation

David S. Aaronson, Ichiro Yamasaki, Alexander Gottschalk, Joycelyn Speight, I-Chow Hsu, Barby Pickett, Mack Roach III, Katsuto Shinohara

### Kaplan-Meier biochemical free survival estimate



Number at risk

24 (1) 17 (2) 5 (0) 0

## **NRG Oncology / RTOG 0526: A Prospective Phase II Trial of Transperineal US-Guided Brachytherapy for Locally Recurrent Prostate Adenocarcinoma Following External Beam Radiotherapy**

**JM Crook MD, P Zhang, TM Pisansky, EJ Trabulsi, MB Amin, W Bice, G Morton, N Pervez, E Vigneault, C Catton, J Michalski, M Roach III ... et al.**

### **NRG/RTOG 0526: Primary endpoint**

- **Predicting that  $\leq 10\%$  of patients would experience a treatment-related grade  $\geq 3$  AE**
- **Rate  $\geq 20\%$  would be considered unacceptable (null hypothesis)**
- **One-sided significance level of 0.05 required an estimated 87 analyzable patients to detect the above-mentioned effect size with an 85% statistical power using Fleming's multiple testing procedure**
- **2 interim analyses and one final analysis**
- **Adjusting by 10% for patients not analyzable due to ineligibility, lost to follow-up, etc., 96 patients required**

## Eligibility: NRG/ RTOG 0526

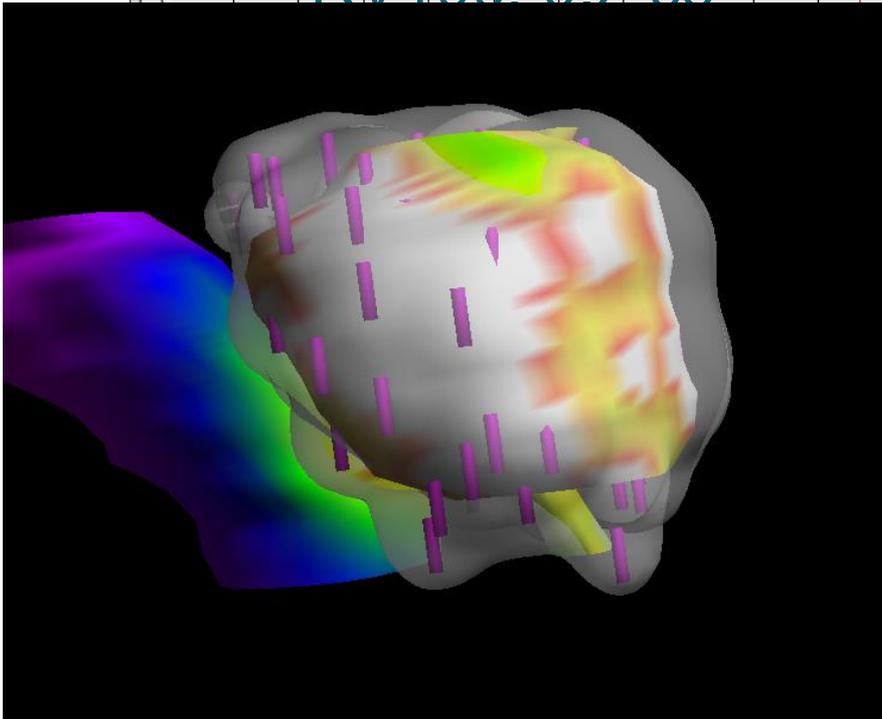
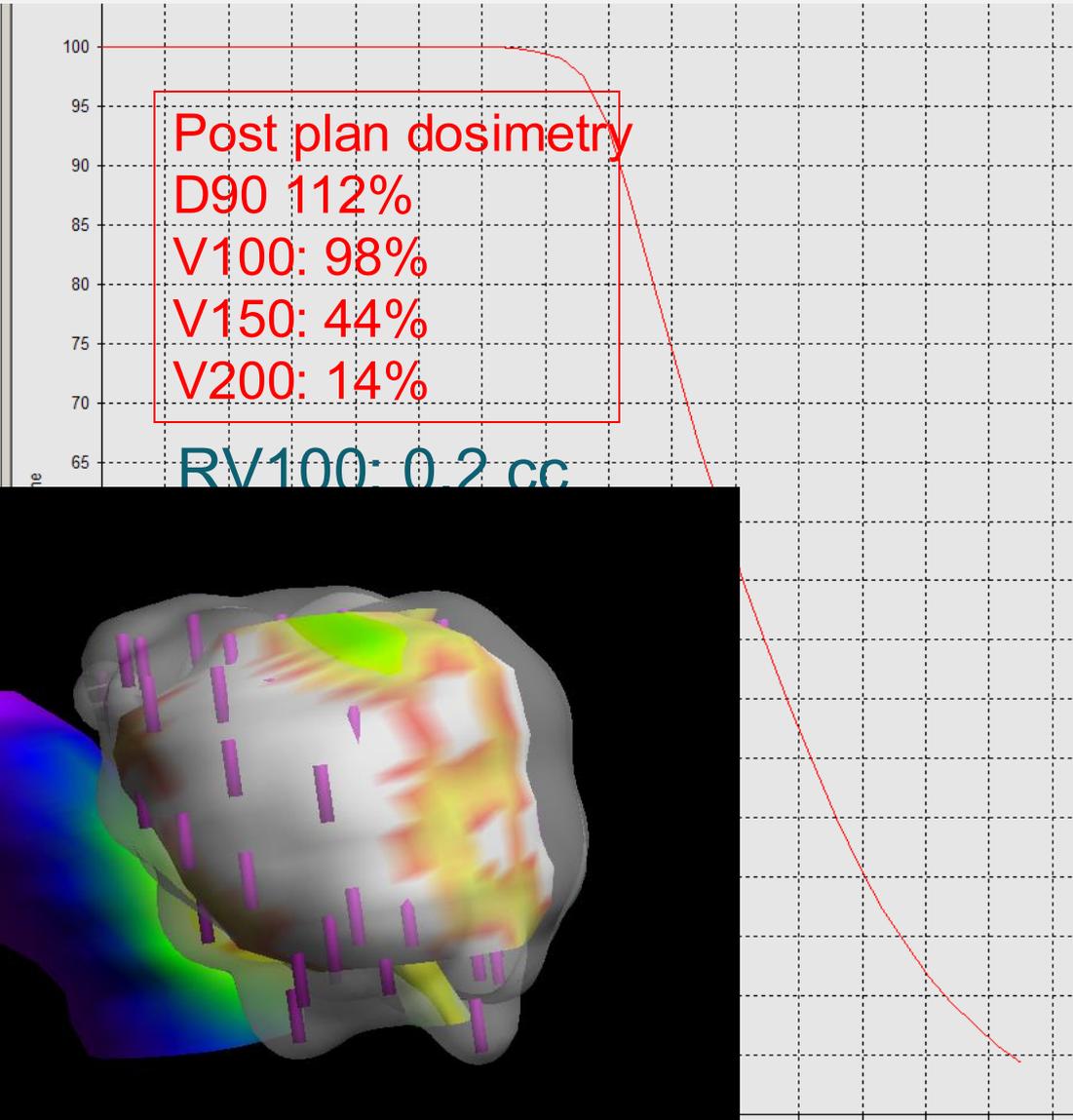
- Initial presentation low or intermediate risk
- > 30 mos after EBRT (up to 78Gy/39 or 81Gy/45)
- Biopsy “positive” < 180 days prior to registration and confirmed by central review
- PSA < 10 ng/ml (within 8 weeks)
- TRUS volume  $\leq$  45 cc
- no GI/GU toxicity  $\geq$  grade 2 (CTCAE V3)
- no prior TURP, HIFU or cryotherapy
- IPSS < 15

Institutional Credentialing required

# Summary of Patient Enrollment

- **Opened to accrual on May 11, 2007**
- **Accrual completed on January 21, 2014**
- **100 patients registered (20 centers)**
  - 8 patients excluded (PSA > 10 ng/ml, no tumor on review, no treatment, < 30 months from EBRT)
- **Analyses focused on the 92 eligible patients who received protocol treatment.**
  - Median age: 70 years.
  - 92% Zubrod performance status 0
  - 48% initial Gleason score 7
  - 84% PSA ≤ 10 ng/ml at baseline.
  - Prostate TRUS volume 25 cc (range 14-44 cc)

# Whole prostate salvage plan



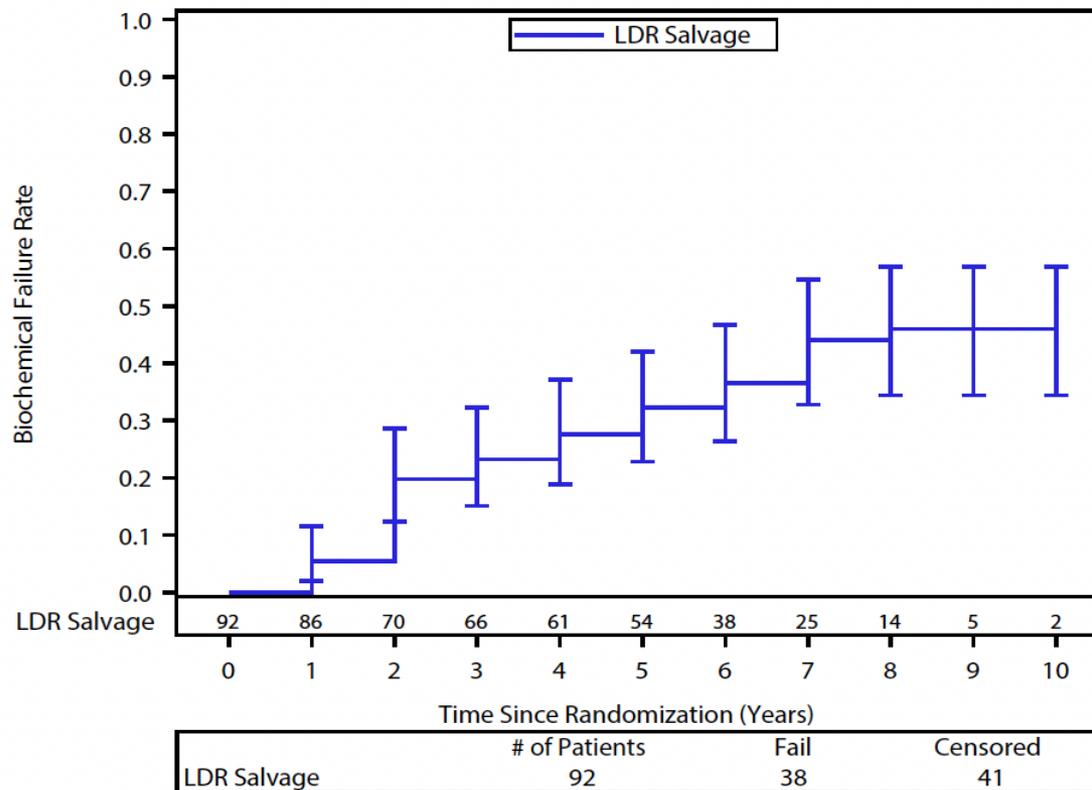
Dose	Prostate				
	%	Cum. DVH cc	%	Diff. DVH cc	%
0.00	0.00	23.86	100.00	0.00	0.00
7.25	5.00	23.86	100.00	0.00	0.00
14.50	10.00	23.86	100.00	0.00	0.00
21.75	15.00	23.86	100.00	0.00	0.00
29.00	20.00	23.86	100.00	0.00	0.00
36.25	25.00	23.86	100.00	0.00	0.00
43.50	30.00	23.86	100.00	0.00	0.00
50.75	35.00	23.86	100.00	0.00	0.00
58.00	40.00	23.86	100.00	0.00	0.00
65.25	45.00	23.86	100.00	0.00	0.00
72.50	50.00	23.86	100.00	0.00	0.00
79.75	55.00	23.86	100.00	0.00	0.00
87.00	60.00	23.86	100.00	0.00	0.00
94.25	65.00	23.86	100.00	0.00	0.00
101.50	70.00	23.86	100.00	0.00	0.00
108.75	75.00	23.86	100.00	0.00	0.00
116.00	80.00	23.86	100.00	0.00	0.00
123.25	85.00	23.85	100.00	0.02	0.10
130.50	90.00	23.83	99.90	0.07	0.31
137.75	95.00	23.76	99.59	0.15	0.63
145.00	100.00	23.61	98.96	0.34	1.44
152.25	105.00	23.28	97.92	0.97	4.07
159.50	110.00	22.29	93.45	1.47	6.16
166.75	115.00	20.82	87.30	1.73	7.25
174.00	120.00	19.09	80.04	1.68	7.05
181.25	125.00	17.41	73.00	1.58	6.63
188.50	130.00	15.83	66.37	1.46	6.14
195.75	135.00	14.37	60.23	1.37	5.76
203.00	140.00	12.99	54.47	1.30	5.43
210.25	145.00	11.70	49.04	1.16	4.85
217.50	150.00	10.54	44.19	1.15	4.83
224.75	155.00	9.38	39.35	1.07	4.47
232.00	160.00	8.32	34.88	0.98	4.09
239.25	165.00	7.35	30.79	0.82	3.44
246.50	170.00	6.53	27.35	0.72	3.02
253.75	175.00	5.81	24.34	0.65	2.73
261.00	180.00	5.15	21.61	0.54	2.28
268.25	185.00	4.61	19.33	0.43	1.81
275.50	190.00	4.18	17.52	0.42	1.75
282.75	195.00	3.78	15.77	0.34	1.41
290.00	200.00	3.42	14.36	0.32	1.35

## Results RTOG 0526

- **Median follow up 54 mo (4-97)**
- **Median EBRT dose 74 Gy (IQR: 70-76)**
- **Interval since EBRT 85 mo (IQR: 60-119)**
- **ADT at time of recurrence: 16%**
- **12 patients with acute grade 3 GI/GU AE's**
- **12 patients with late grade 3 GI/GU AE's**
- **No grade 4 or 5**

## CLINICAL INVESTIGATION

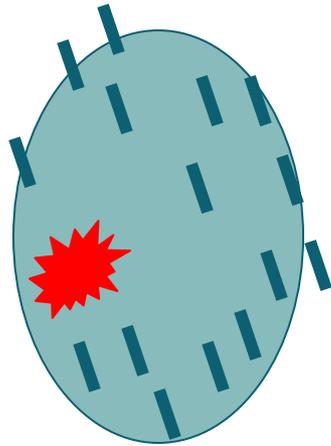
# Salvage Low-Dose-Rate Prostate Brachytherapy: Clinical Outcomes of a Phase 2 Trial for Local Recurrence after External Beam Radiation Therapy (NRG Oncology/RTOG 0526)



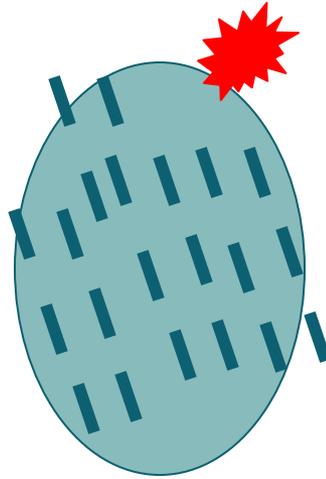
**Fig. 4.** Actuarial rate of biochemical failure after low-dose-rate salvage brachytherapy, with numbers of patients at risk shown above the x-axis.

Local

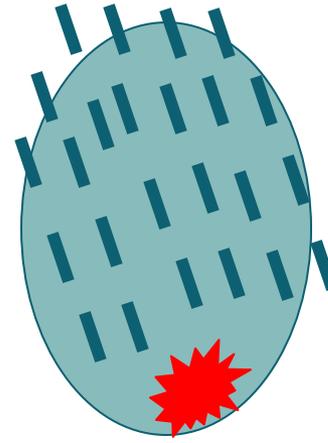
EXAMPLES OF TYPES OF PSA LOCAL FAILURES



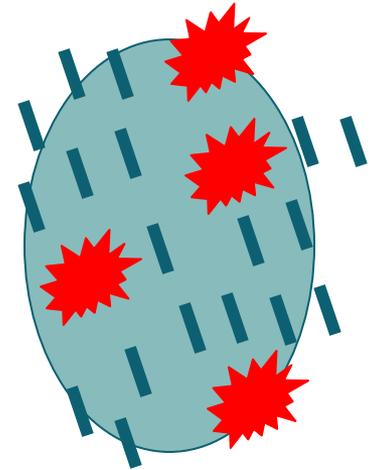
Focal e.g. due to Inadequate Dose ("T1c")



Marginal Failure ("T3")



"Cold spot"  
(small vs large)



Diffuse Failure

Salvage RP

++

+

+/-

+/-

Cryo

++

++

+

-

Hi-Fu

+

+

?

-

PPI/HDR

++?

-/++

++/+

-/+?

Other?

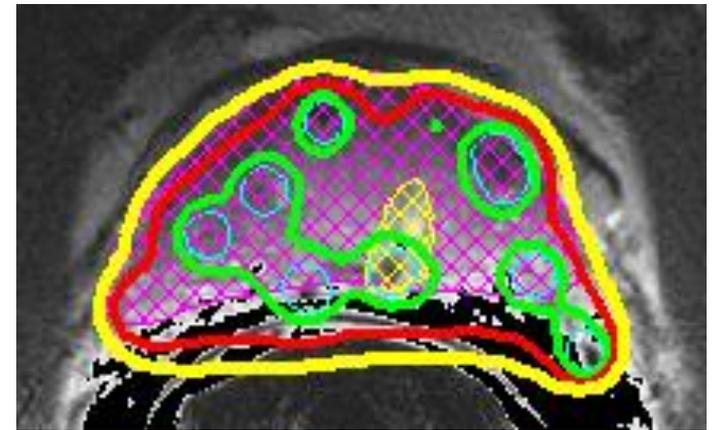
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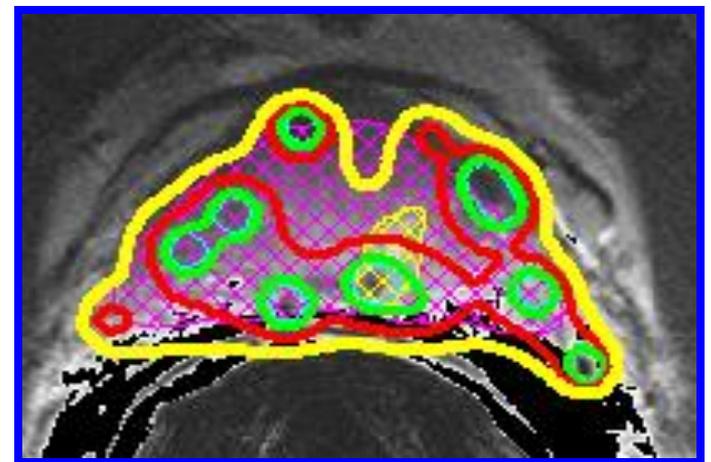
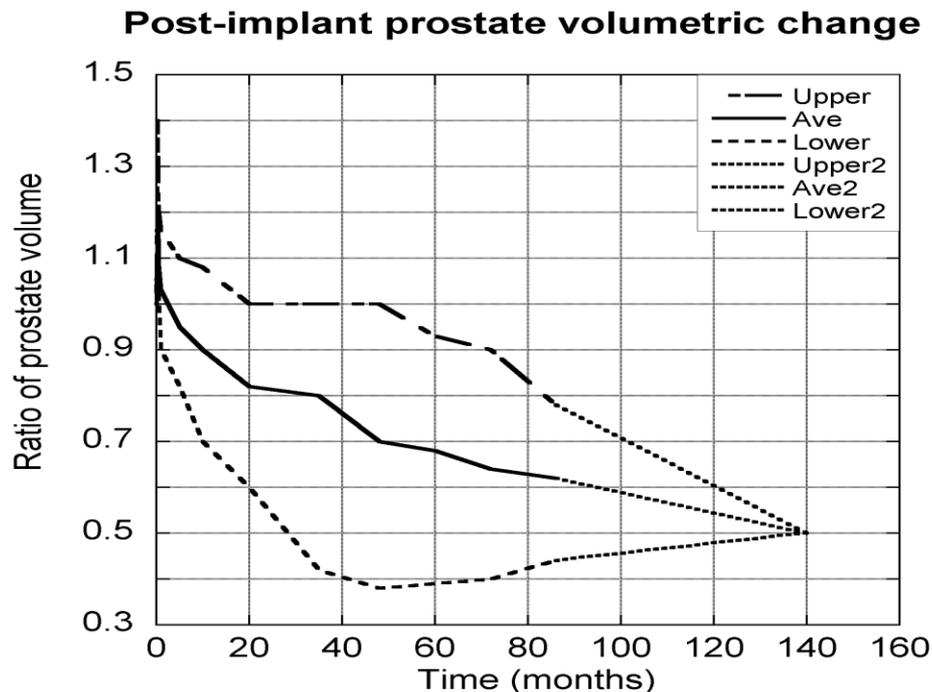
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**Feasibility of MR Imaging /MR Spectroscopy-  
Planned Focal Partial Salvage Salvage  
Permanent Prostate Implant (PPI) for Localized  
Recurrence After Initial PPI for Prostate Cancer.  
Hsu, Hsu, Pickett ... Roach IJROBP 2012**



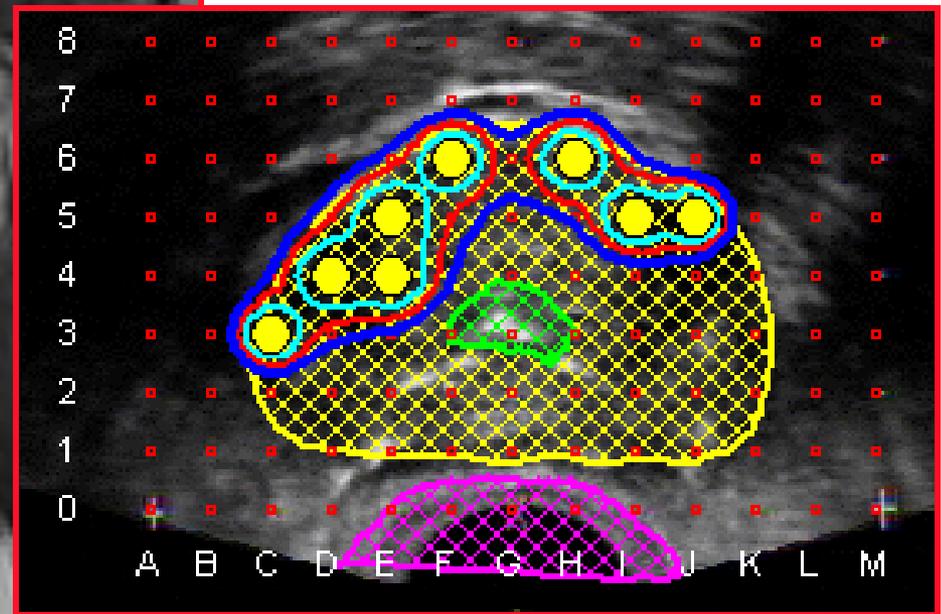
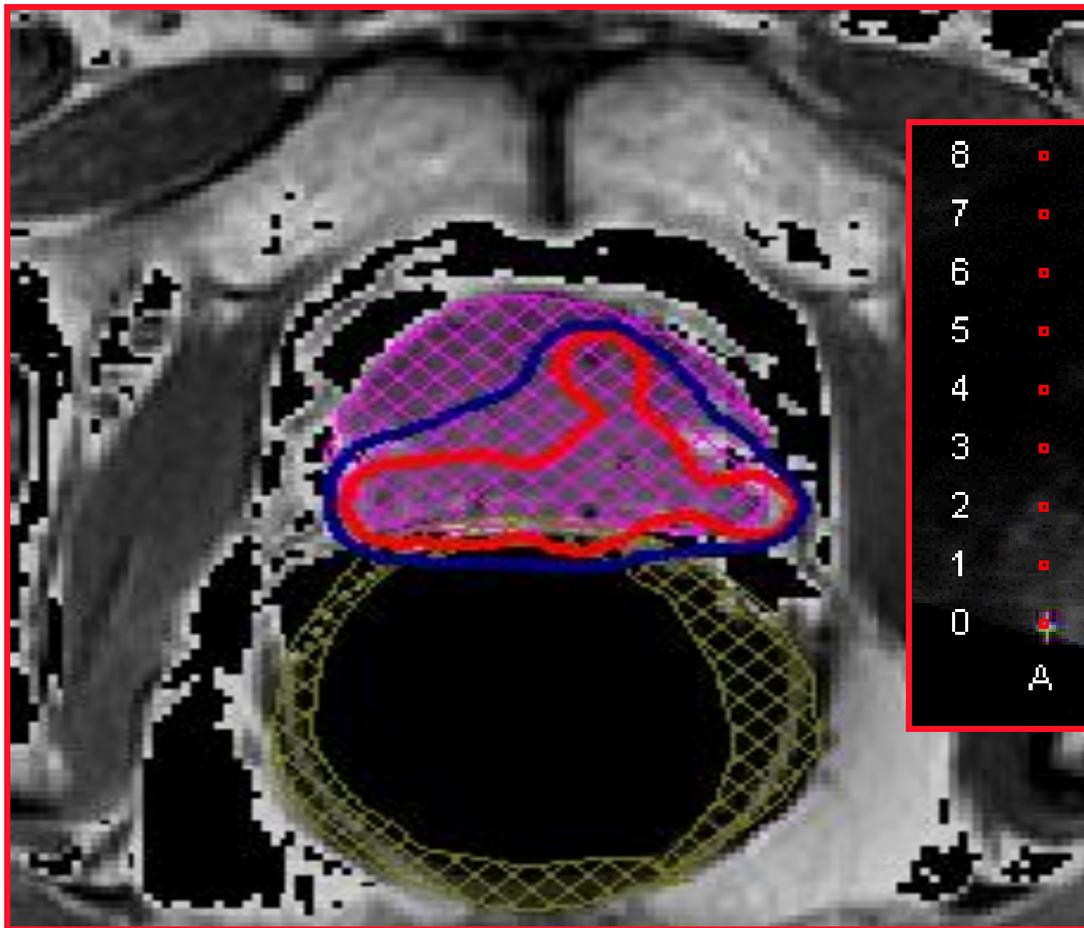
**Step 1: Review current MRI - note image is smaller than the original MR**

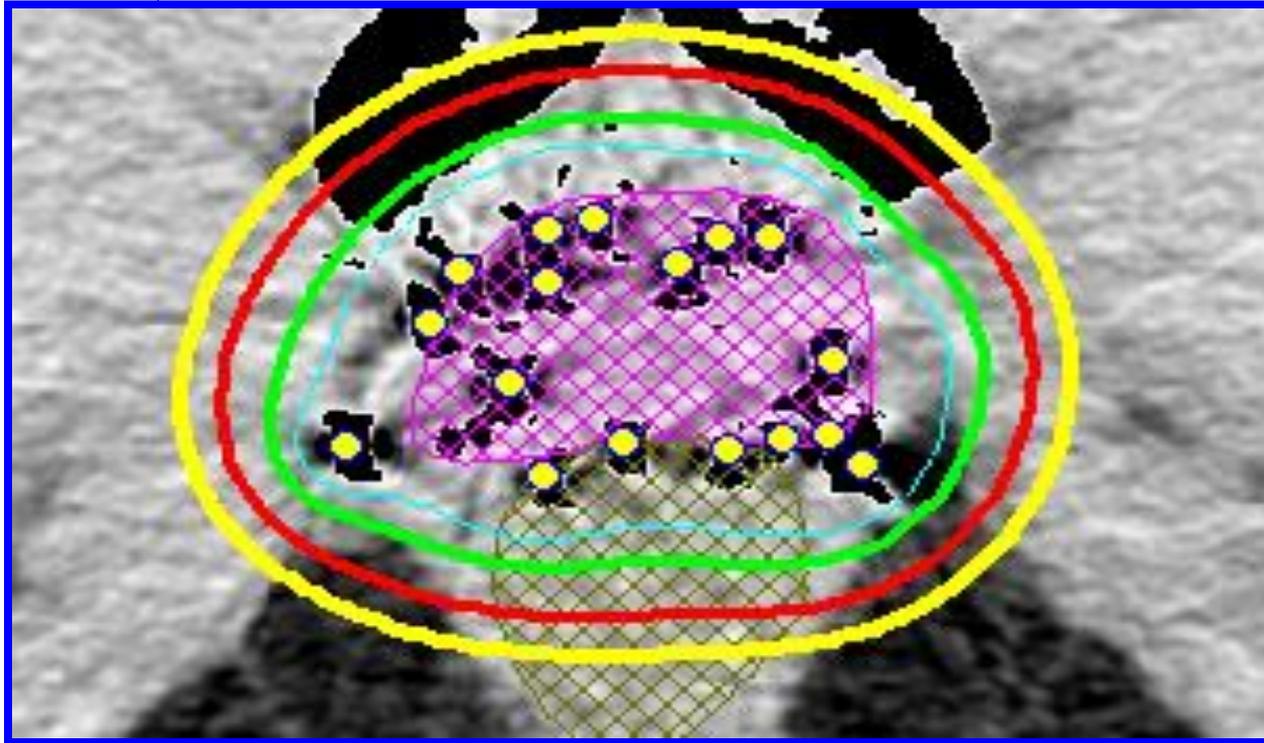


**Step 2: Use shrinkage curve to determine ratio of current volume vs. size at time of original implant and recreate the initial treatment**

# Feasibility of MR Imaging /MR Spectroscopy-Planned Focal Partial Salvage Salvage Permanent Prostate Implant (PPI) for Localized Recurrence After Initial PPI for Prostate Cancer.

Hsu, Hsu, Pickett ... Roach IJROBP 2012

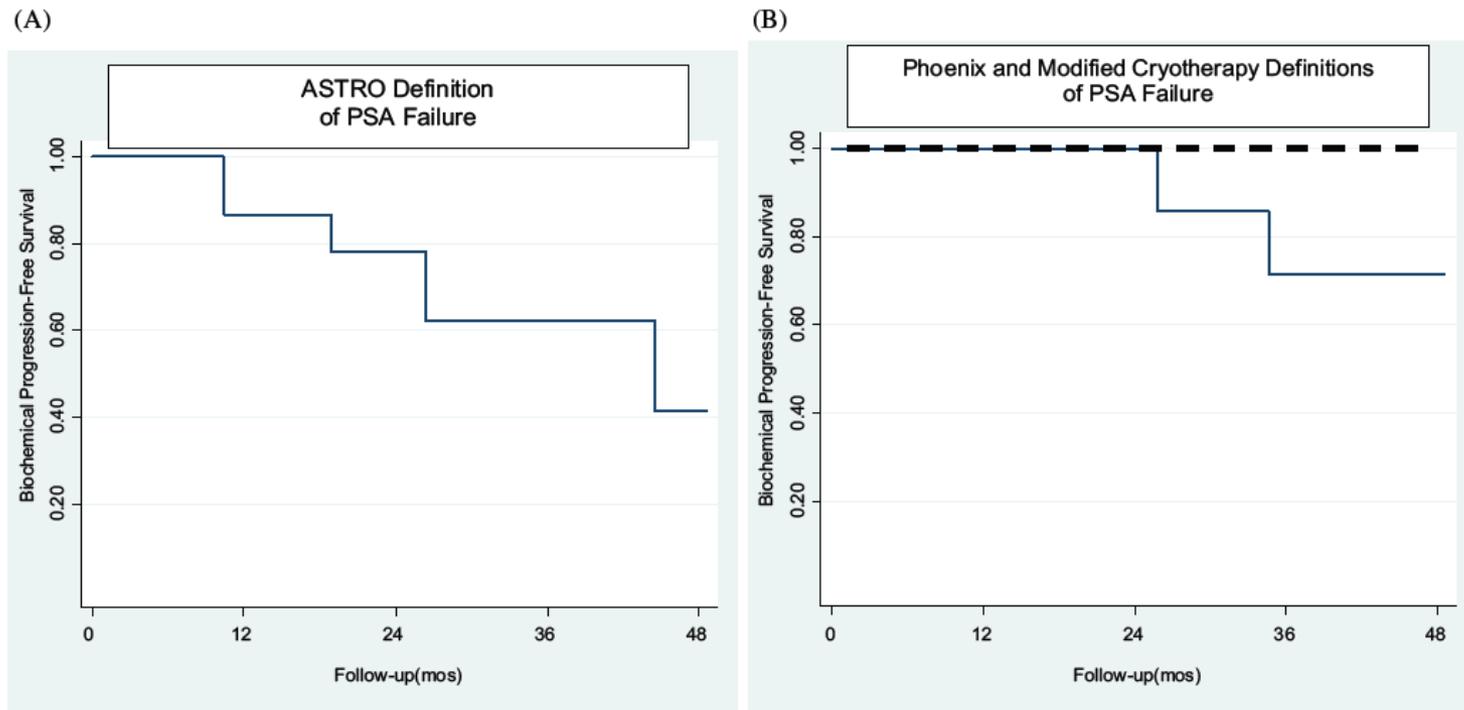




**Confirm implementation of salvage plan  
on CT with composite plan with  
appropriate DVHs**

# Feasibility of MR Imaging /MR Spectroscopy-Planned Focal Partial Salvage Salvage Permanent Prostate Implant (PPI) for Localized Recurrence After Initial PPI for Prostate Cancer.

Hsu, Hsu, Pickett ... Roach IJROBP 2012

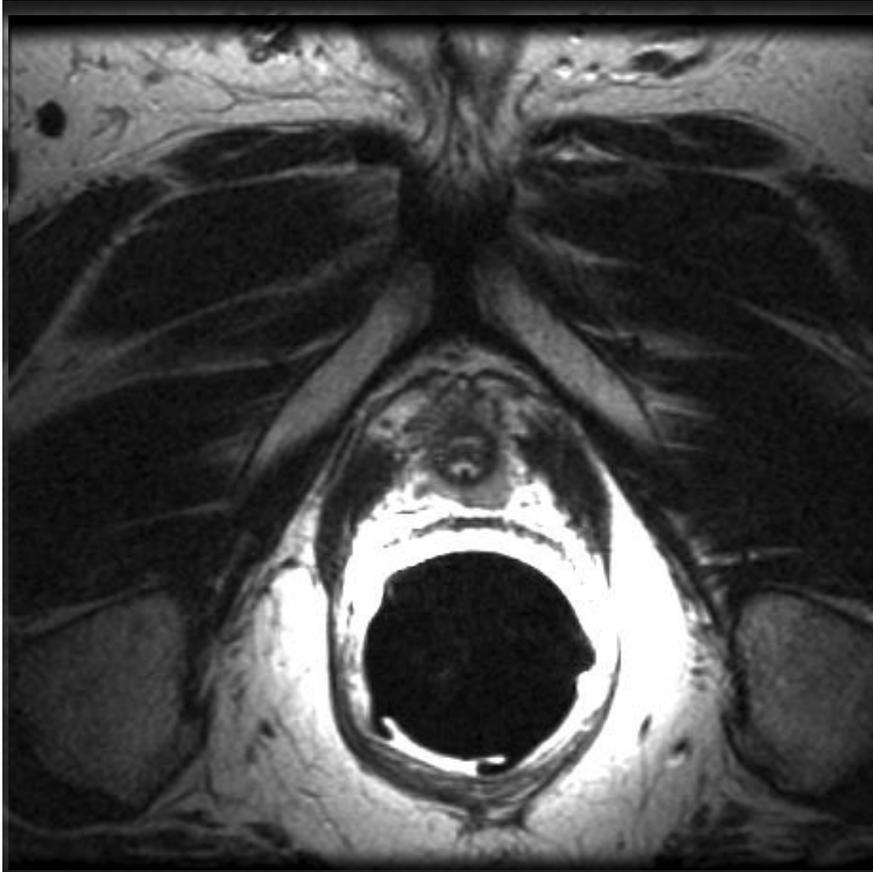


**Fig. 3.** PFS estimates for psPPI. (A) ASTRO-PFS and (B) Phoenix-PFS (solid line) N=2 biopsy-proven recurrence at 26 and 35 months. Modified CRYO-PFS (dashed line) with successful repeat psPPI performed at biopsy-proven recurrence (N=2).

## Case 1

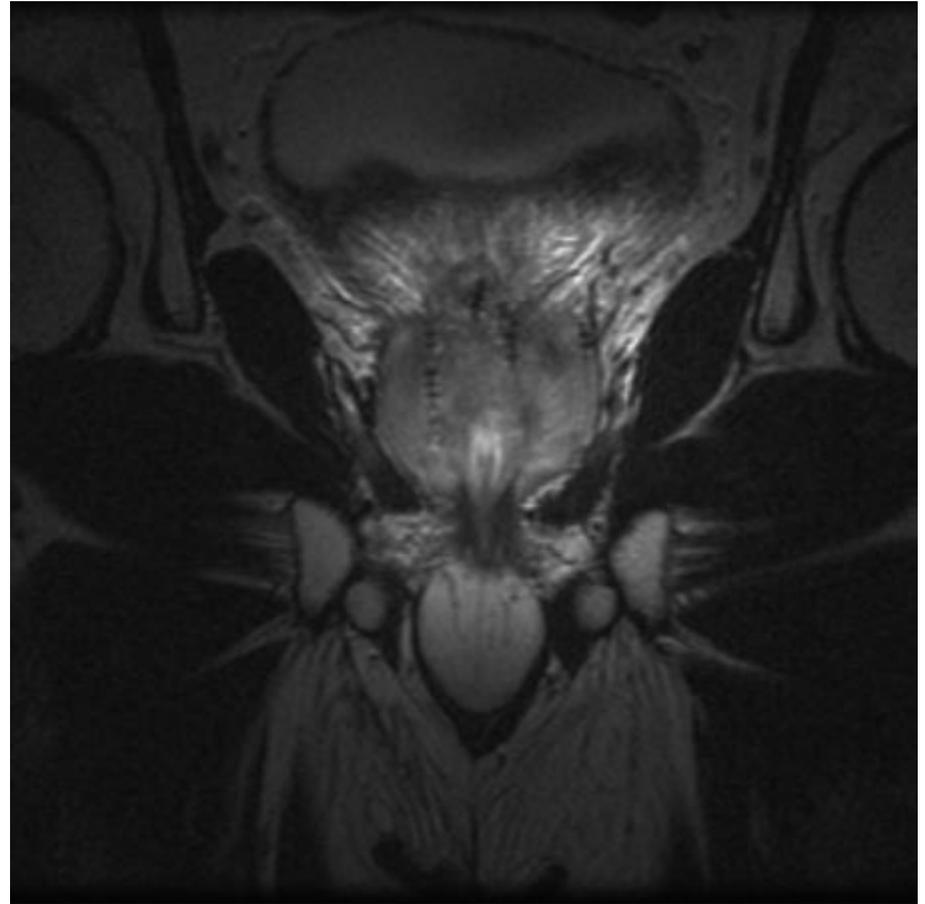
- **56 yo man s/p Pd-103 implant followed by 45 Gy of XRT and neo-adjuvant hormone therapy in 1998**
- **PSA 5.6, Gleason 3+3 apex involvement**
- **PSA gradually rose upto 1.6**
- **Biopsy Gleason 4+3, 7 mm at L apex**

# MRSI Imaging after Brachytherapy



Example of poorly covered apex

# MRSI Imaging after Brachytherapy



Example of poorly covered apex

Scan Date : 10/14/2002  
 Image File : pc3556\_E18520S3\_div.int2  
 CSI File : pc3556b\_cor\_rephased.cmplx

# MRSC/UCSF Proton MRS Study

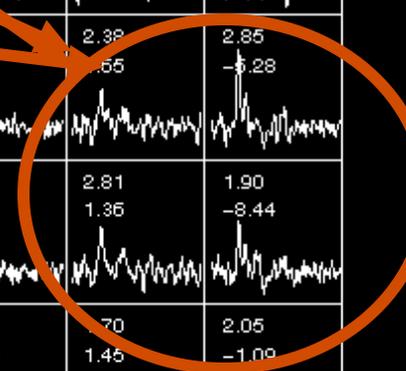
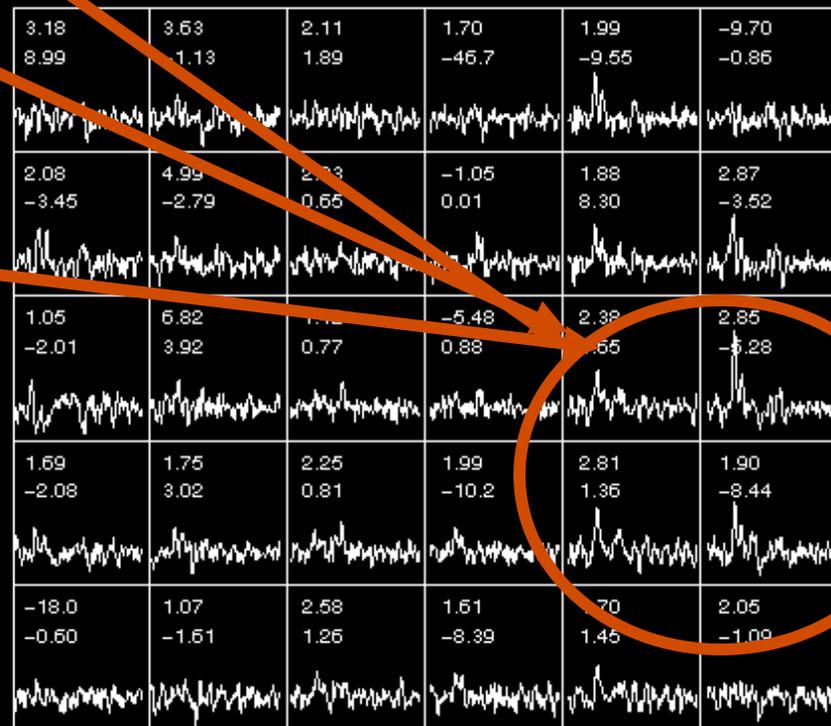
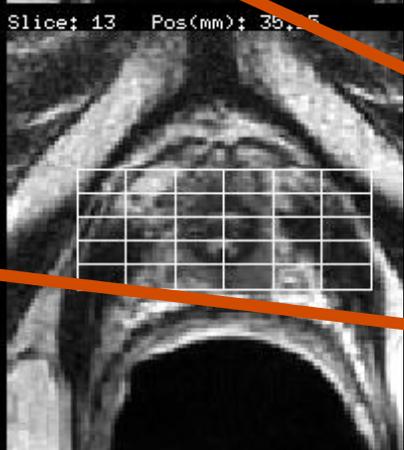
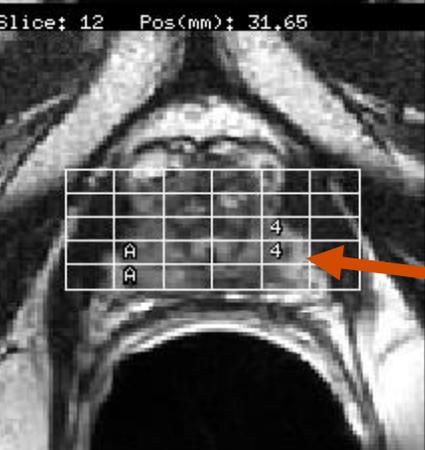
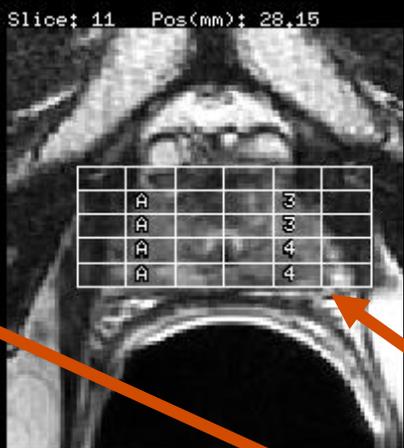
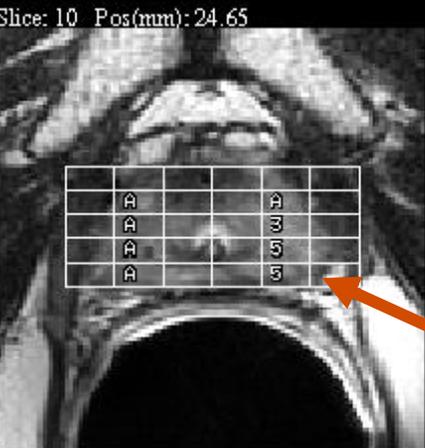
Patient ID : 43942875  
 Scan Date : 10/14/2002

Image File : pc3556\_E18520S3\_div.int2  
 Image Series : 103  
 Image FOV : 61.80 X 61.80  
 Image Coil : PELVIC

CSI File : pc3556b\_cor\_rephased.cmplx  
 CSI Slice No. : 11  
 CSI Slice Pos. : 28.15 mm  
 Coil : PELVIC  
 TE : 130 ms

Selected Region : 24.72 cc  
 Size : 41.2 RL 20.0 AP 30.0 SI mm  
 Center : 4.0 RL -18.3 AP 19.4 SI mm  
 CSI Resolution : 0.09 cc  
 Size : 7.0 RL 3.5 AP 3.5 SI mm  
 Center : 4.0 RL -14.8 AP 19.4 SI mm

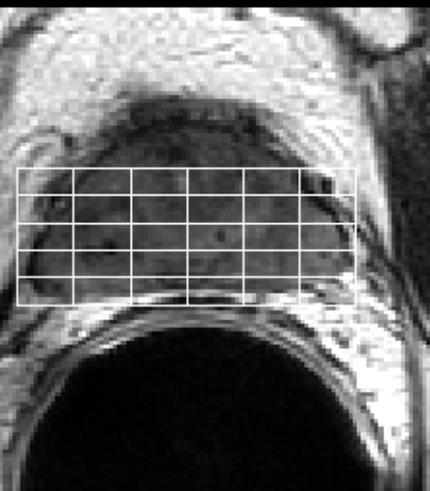
Ch/Cr CC/C



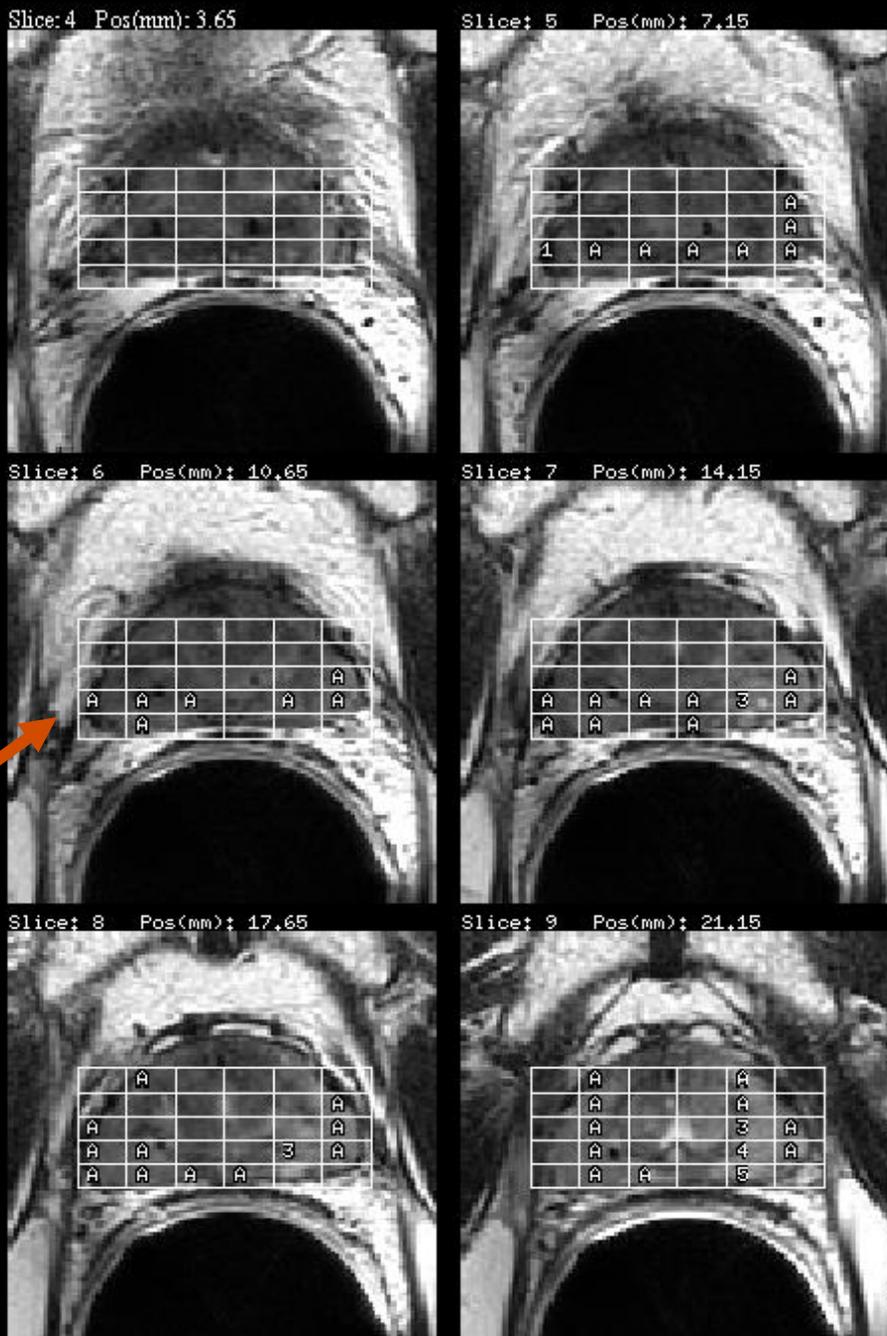
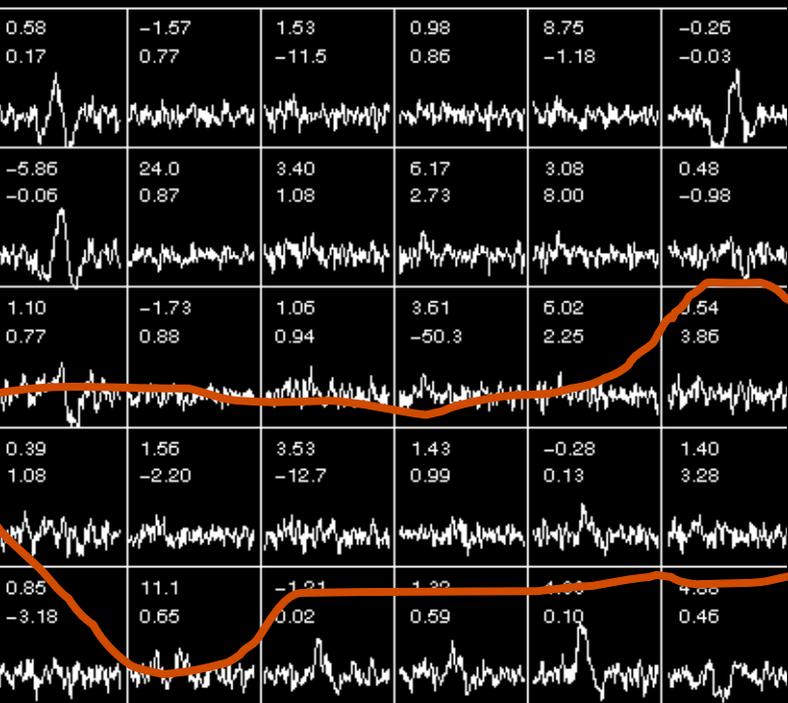
# MRSC/UCSF Proton MRS Study

MRSC/UCSF Proton MRS Study  
 Scan Date : 10/14/2002  
 Image File : pc3556\_E18520S3\_div.int2  
 CSI File : pc3556b\_cor\_rephased.cmplx  
 Size : 41.2 RL 20.0 AP 30.0 SI mm  
 CSI Resolution : 0.09 cc  
 Size : 7.0 RL 3.5 AP 3.5 SI mm

Patient ID : 43942875  
 Scan Date : 10/14/2002  
 Image File : pc3556\_E18520S3\_c  
 Image Series : 103  
 Image FOV : 61.80 X 61.80  
 Image Coil : PELVIC  
 CSI File : pc3556b\_cor\_rephas  
 CSI Slice No. : 6  
 CSI Slice Pos. : 10.65 mm  
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 TE : 130 ms  
 Selected Region : 24.72 cc  
 Size : 41.2 RL 20.0 AP 30.0 SI mm  
 Center : 4.0 RL -18.3 AP 19.4 SI m  
 CSI Resolution : 0.09 cc  
 Size : 7.0 RL 3.5 AP 3.5 SI mm  
 Center : 4.0 RL -14.8 AP 19.4 SI m

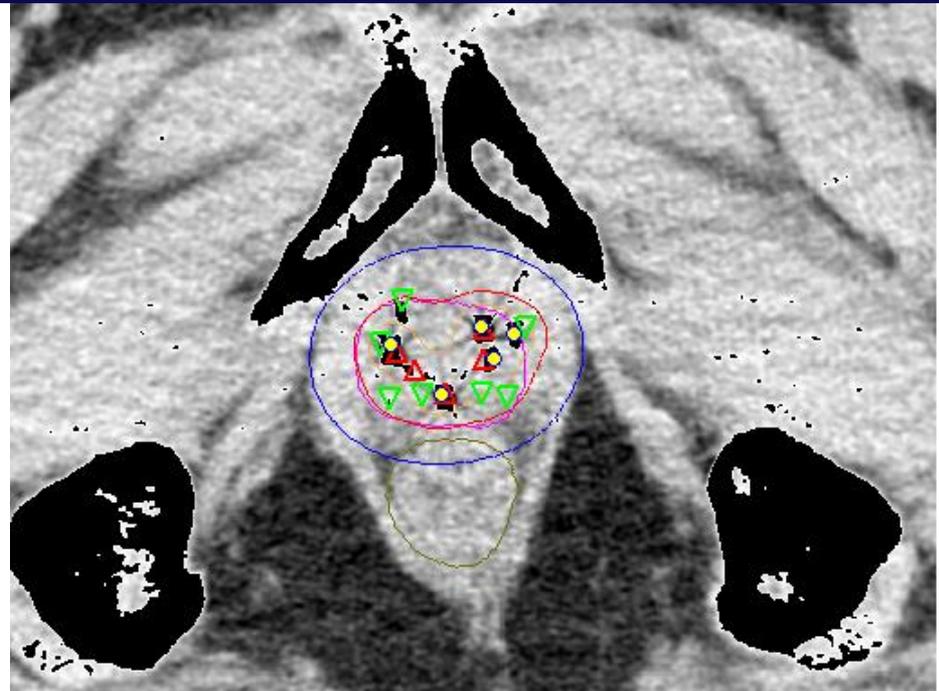
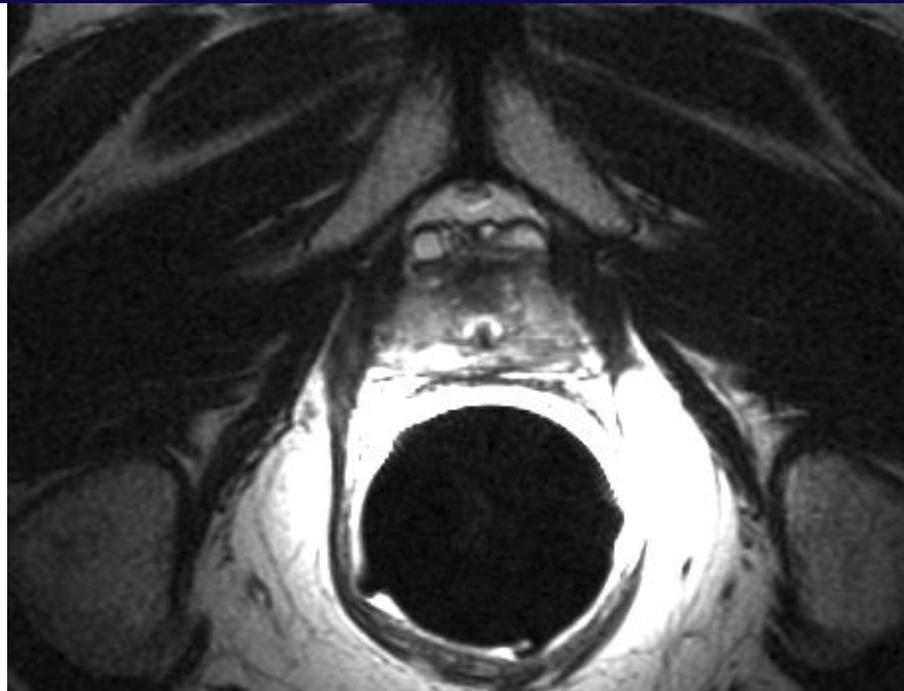


Ch/Cr CC/C

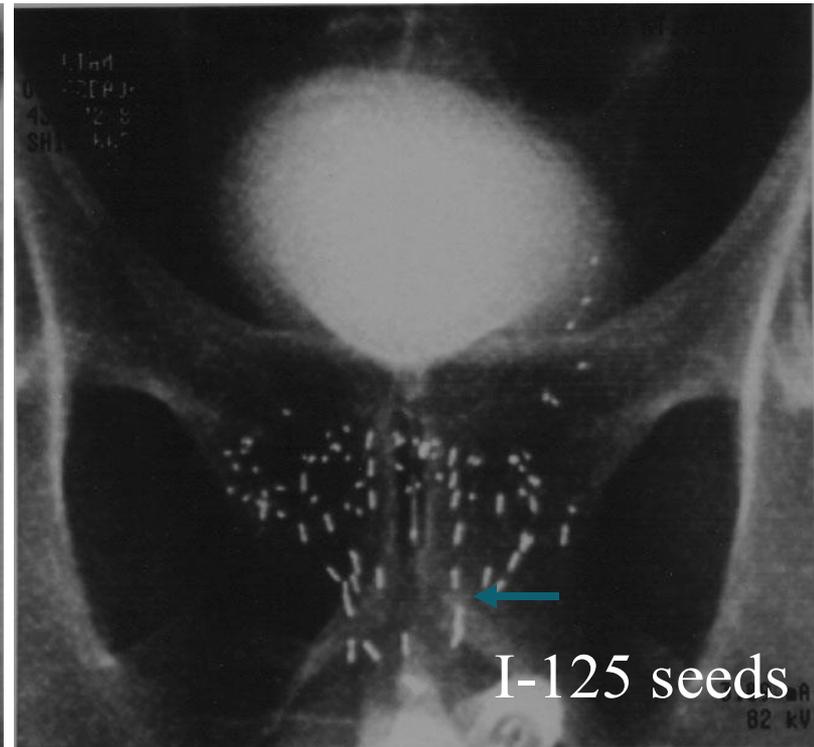
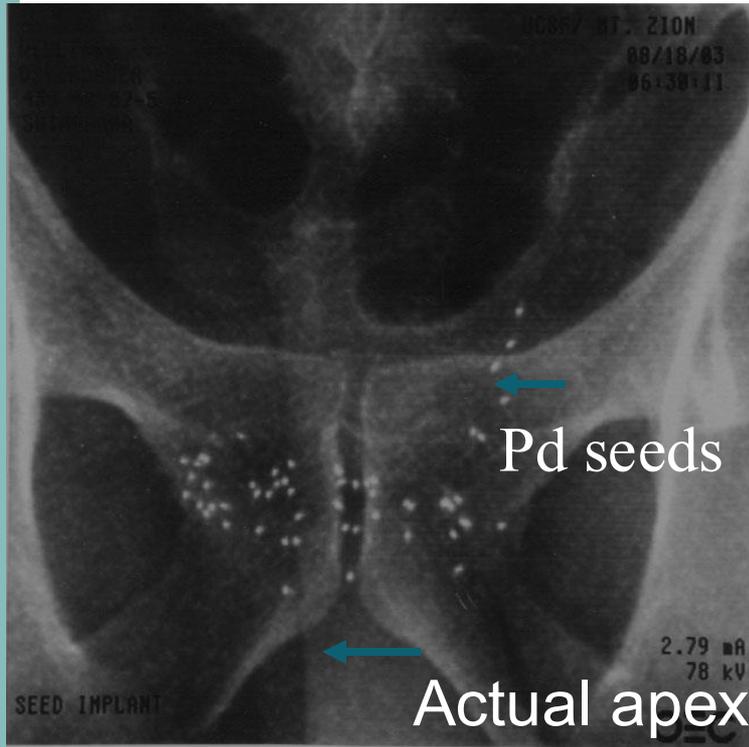


- 1=Def Nor
- 2=Prob No
- 3=Equivo
- 4=Prob Ab
- 5=Def Abn
- A=Atrophy
- U=Un-usa
- B=Biop Ar

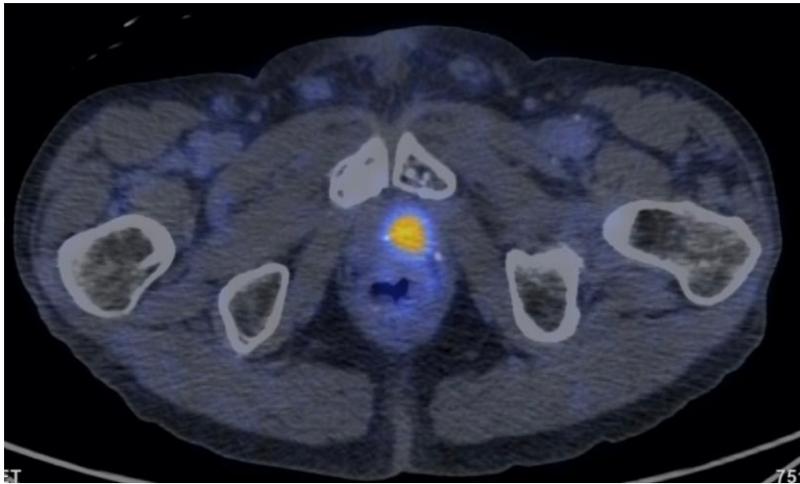
# Pre-Salvage MRSI Imaging & CT Post Brachytherapy



# SALVAGE BRACHYTHERAPY After primary brachytherapy



9/20/24 (13 yrs later) obstructive symptoms, PSA up to 0.217 ng/mL and PSMA PET shows “hot spot” in the left lobe, Bx GS=4+4 left lobe.

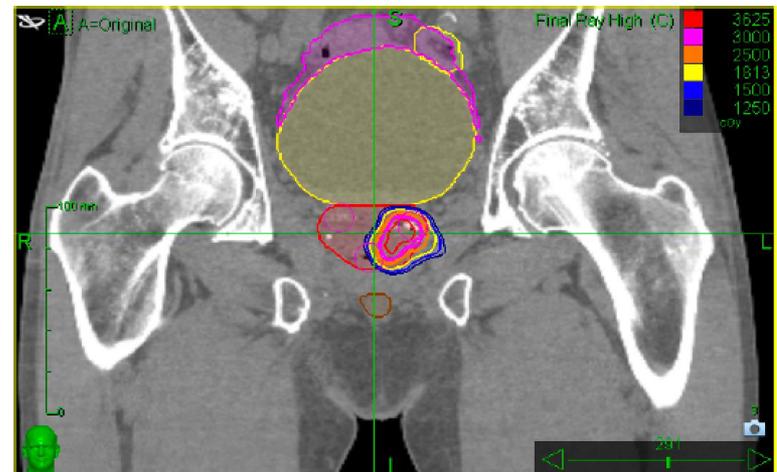


**Plan:**

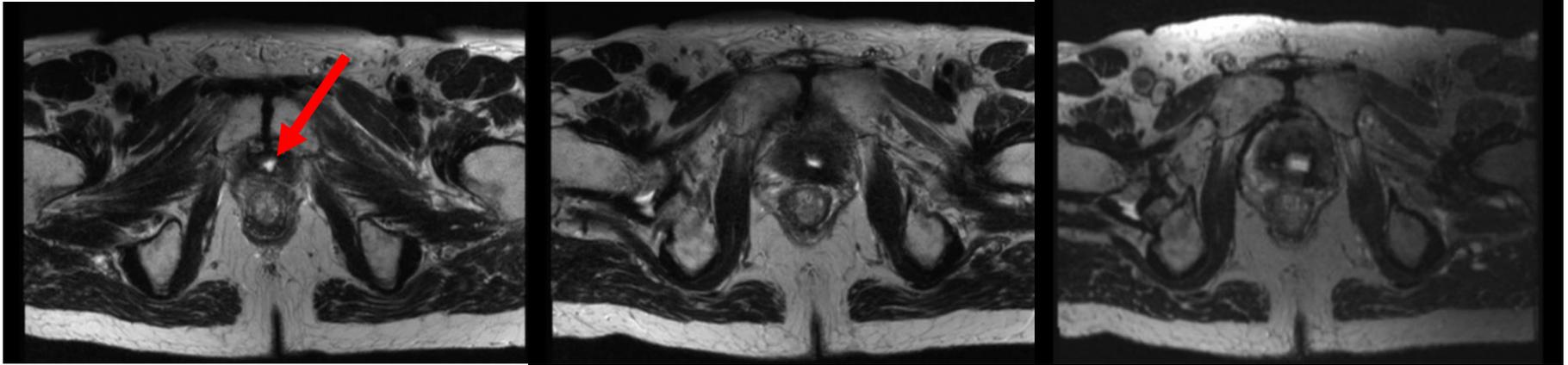
**SBRT 725 x 5 to the DIL**

**followed by Adjuvant ADT.**

**Treatment well tolerated.**

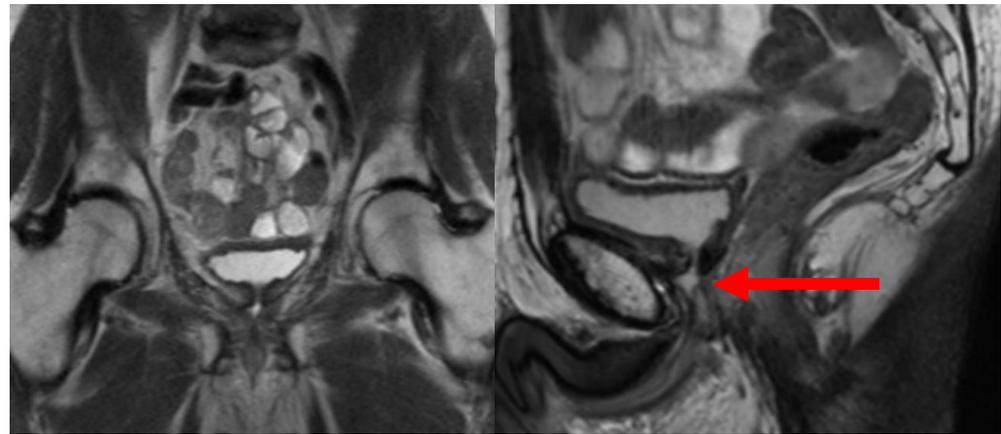


Treatment planning for “Salvage Re-irradiation” has situations when determining what images are is not enough (e.g., TURP defects)



## Concerns:

1. Fistulas
2. Strictures.
3. Sub-urethral necrosis, with calcification and incontinence



Coronal and sagittal images (see the “no-fly zone” **red arrow**)

# “STICK-UP” for patients:

1. Selection
  - a) Phoenix Failure inadequate.
  - b) Bx proven, Negative metastatic w/u (PSMA PET!)
  - c) Unilateral /Focal Disease best
2. Technology
  - a) Composite dose distributions ...
3. Information
  - a) Details of prior RT
4. Cautiously
  - a) “no fly zone”
5. Know
  - a) Anatomy
  - b) “Know what you don’t know”
  - c) Presence of post RT morbidity
6. Urethra
  - a) Respect this organ, fistulas are QoL ruining
7. Plan:
  - a) Constraints based on ALL of above”

# Conclusions concerning re-irradiation for prostate cancer:

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1. In selected pts well executed salvage RT results in high control rates with modest toxicity, less severe than RP & more effective than Cryosurgery.
2. Whole Gland salvage is dangerous and may be less successful *if required*. **Caution.**
3. Sophisticated imaging & planning expertise (e.g., composite plans, dose constraints critical) required.
4. PPI, HDR and SBRT or Proton Beam Radiation can all be effective when appropriately used. Consider “*conservative fractionation*” (e.g., weekly vs EOD)?
5. More trials are needed with biomarkers included.
6. “STICK-UP” for pts and “... at least do no harm ...”

# Acknowledgements

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University of California  
San Francisco

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