

Salvage brachytherapy for locally recurrent prostate cancer

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Case presentation

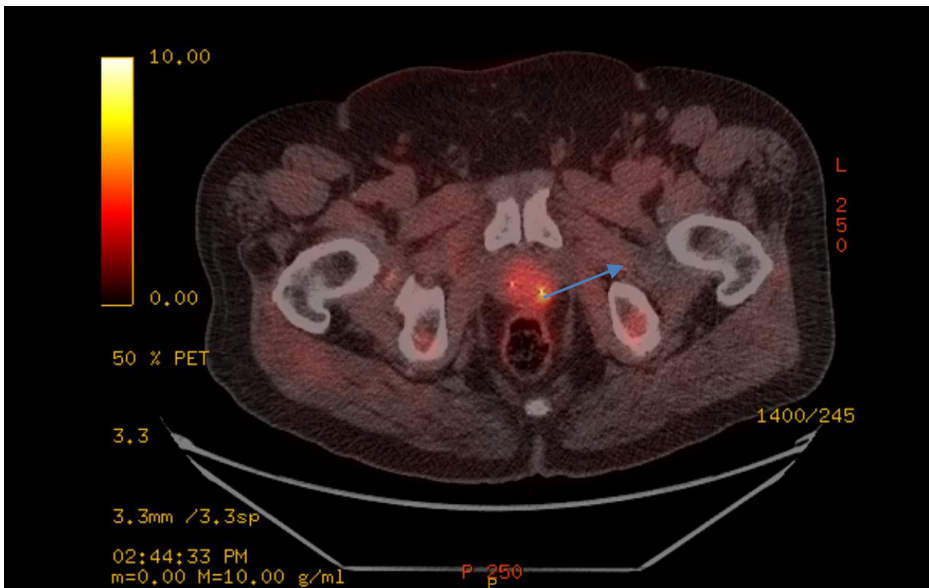
- 73-year-old gentleman was noted to have an elevated PSA of 7.2 on surveillance screening in 2014
- TRUS guided biopsy showed adenocarcinoma of the prostate, cT1c, Gleason 3+4, 3/12 cores positive, iPSA 7.2
- Diagnosed with favorable intermediate risk prostate cancer
- Treated with proton radiation 79.42 cobalt gray equivalents in 44 fractions completed in 12/2014

PSA dynamics

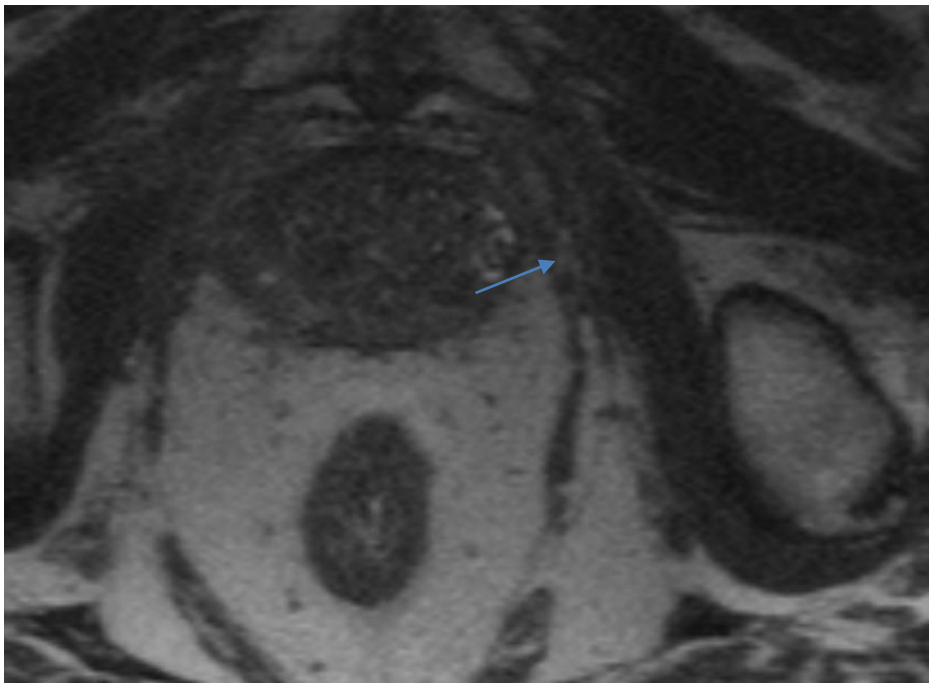
Date	PSA levels ng/ml
4/2014	7.2(pre-treatment PSA)
3/2015	5.3
6/2015	3.2
12/2015	2.1
6/2016	1.95(nadir)
1/2017	2.19
1/2018	2.79
1/2019	4.0(Biochemical recurrence) Phoenix definition of nadir+2
4/2020	4.15

Imaging workup

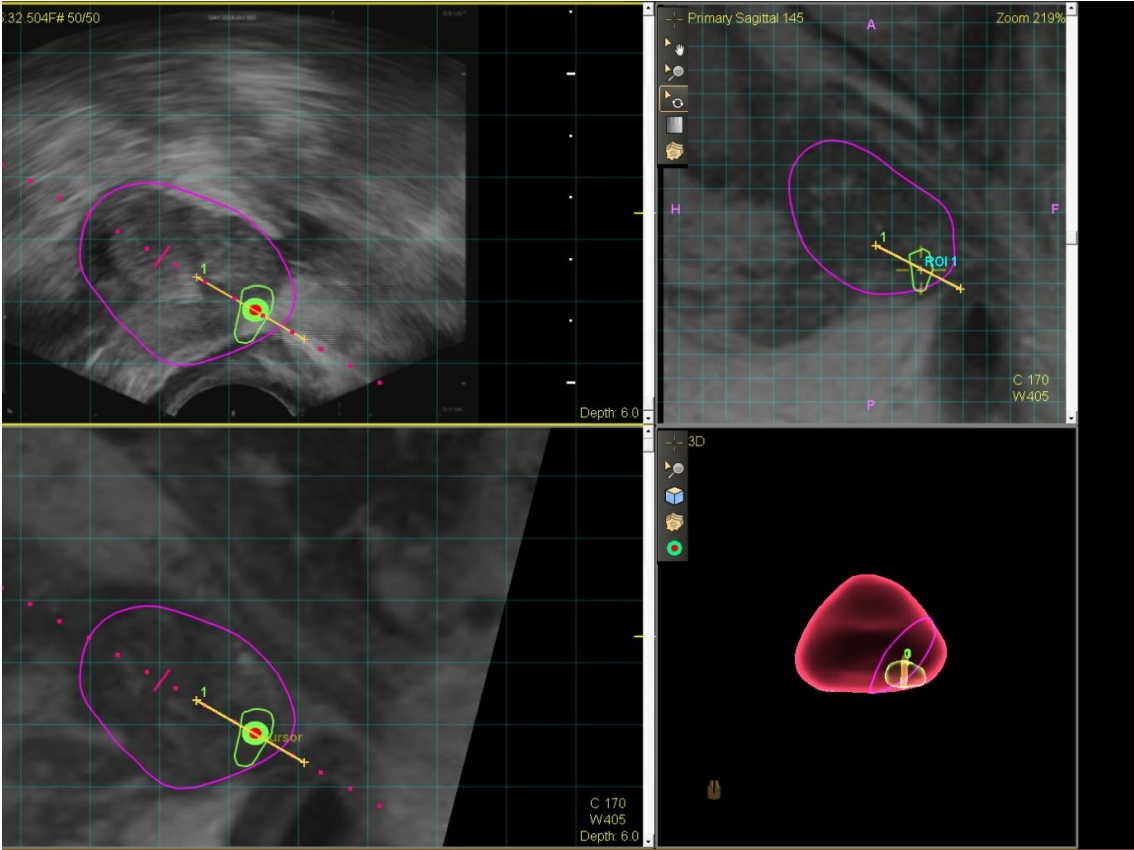
Fluciclovine PET showing Left mid gland posterolateral uptake, extending into apex suggestive of local recurrence



MRI prostate: T2 with 3D reconstruction shows Discrete, homogeneous low signal intensity focus with broad contact with the capsule PI-RADS score: 4 - High (clinically significant cancer is likely to be present)



MRI fusion biopsy



TRUS with MRI fusion uronav biopsy showing adenocarcinoma of prostate in the left mid, left base and left posterolateral lesion with GS of 4+5 involving 4/12 cores positive

The biopsy involves whole gland with mapping biopsy of the index lesion

Treatment options for local recurrence

1. Continued surveillance

2. Palliative ADT

3. Salvage Local Therapy

- ✓ Brachytherapy-HDR,LDR
- ✓ SBRT
- ✓ Cryotherapy
- ✓ High intensity focused Ultrasound
- ✓ Prostatectomy

Why salvage local therapy? why not just ADT

Table. Major Side Effects Associated With Androgen Deprivation Therapy (ADT)

Symptom	Comments
Hot flushes	Very common. Can be mitigated by use of medications such as venlafaxine or gabapentin. Additionally, acupuncture has a potential role in alleviating symptoms.
Osteoporosis	Very common. Estimated 1%–3% fracture risk per year. Men should be given calcium/vitamin D supplements. There is a clear role for osteoclast inhibitors (either zoledronic acid or denosumab) in men with metastatic castration-resistant prostate cancer with bone metastases in preventing skeletal-related events. In men with metastatic castration-sensitive prostate cancer, bisphosphonates have not been shown to be beneficial.
Fatigue	Very common. Seen in most men receiving ADT and independent of anemia or depression. Regular exercise can be beneficial in these patients.
Depression	Common. Seen frequently in men treated with ADT and should be explored at multiple visits. May be amenable to treatment with SSRI (or SNRI if concurrent with hot flushes).
Gynecomastia	Common. Can be a major quality of life issue, although tamoxifen and radiotherapy can be potential treatment options.
Erectile dysfunction	Common. Both erectile dysfunction and decreased libido are seen in men receiving ADT and remain major quality-of-life issues. Referral to sexual health counseling may be of benefit.
Metabolic syndrome	Common. Weight gain is commonly seen within 1 year of starting ADT. Additionally, insulin resistance, dyslipidemia, and sarcopenic obesity are reported.
Dementia	Controversial. Multiple studies have explored this issue, with mixed and conflicting findings. This remains an active area of clinical research.
Thromboembolic disease	Controversial. Several meta-analyses have shown an association between VTE and ongoing ADT use, though many have not controlled for ongoing tobacco use and acute hospitalizations, both of which increase thrombotic risk.
Cardiovascular disease	Controversial. Several meta-analyses have found conflicting results on risk of cardiovascular disease from ADT. Primary and secondary prevention for cardiovascular disease should be pursued.

SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; VTE = venous thromboembolism.

- ✓ Patient elected to proceed with salvage brachytherapy
- ✓ At our institution we have a phase 2 trial of Focal salvage HDR brachytherapy for locally recurrent prostate cancer in patients treated with prior radiotherapy (F-Sharp trial)
- ✓ Why focal therapy: Can potentially reduce urinary and sexual toxicity and target the areas of local recurrence alone

- ✓ Day care procedure: Patient has perineal needles placed under TRUS guidance under general anesthesia.(30-45min)
- ✓ CT simulation and MRI prostate done. The diagnostic PET and MRI are also fused.
- ✓ The biopsy proven area of local recurrence with correlative imaging findings are contoured to form GTV. GTV+5mm margin forms the CTV.
- ✓ CTV is prescribed a dose of 13.5Gy with GTV run hot with dose ranging from 15-17Gy.
- ✓ Second implant done 1-2 weeks apart

Planning dose constraints

Priority will be given to the normal tissue dose constraints over the prescription dose.

Priority will be given to GTV coverage first and then CTV coverage.

GTV (V100 \geq 95%)

GTV (D90 \geq 100%)

CTV (V100 \geq 95%)

CTV (D90 \geq 100%)

The normal tissue dose constraints will be as follows:

Bladder: D 0.1 cc \leq 12.82 Gy , D 1cc \leq 10.13 Gy , V10.13 Gy \leq 1 cc

Rectum: D 1 cc \leq 10.13 Gy Gy , V10.13 Gy \leq 1 cc

Urethra: Max point dose \leq 16.2 Gy, D 1 cc \leq 14.85 Gy

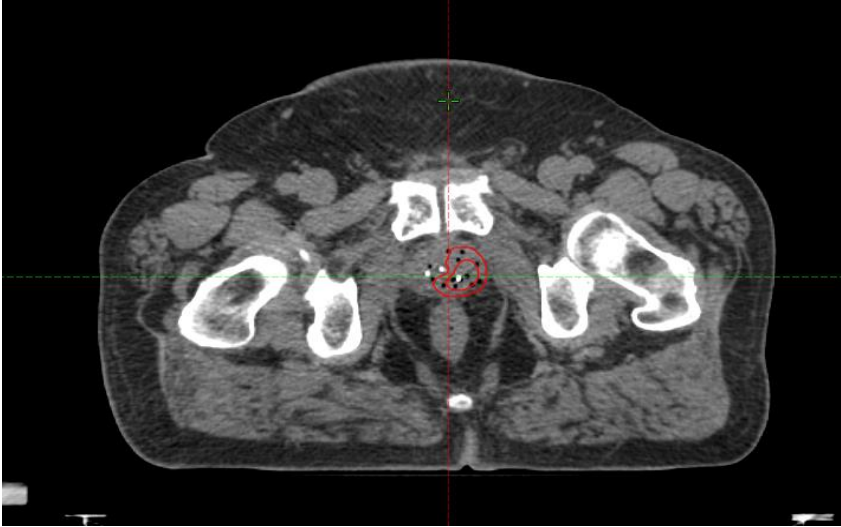


Figure 1 shows the CT contours with inner red line is the GTV and the outer red line is the CTV

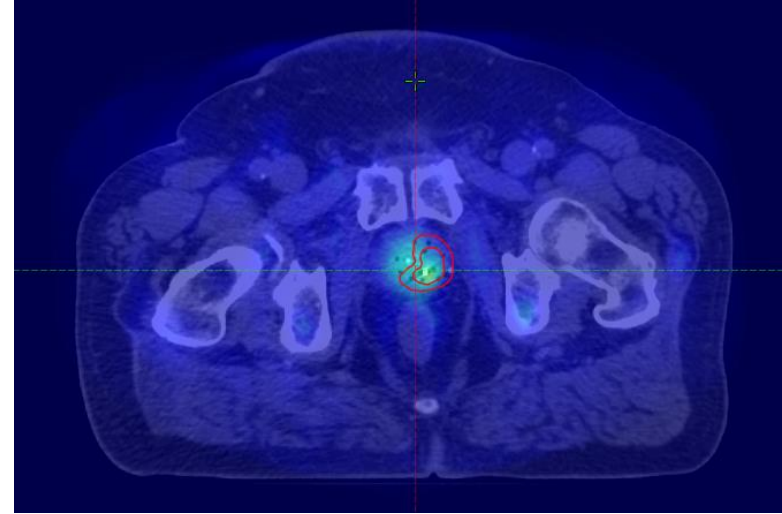


Figure 2 corresponding PET contours with inner red line is the GTV and the outer red line is the CTV

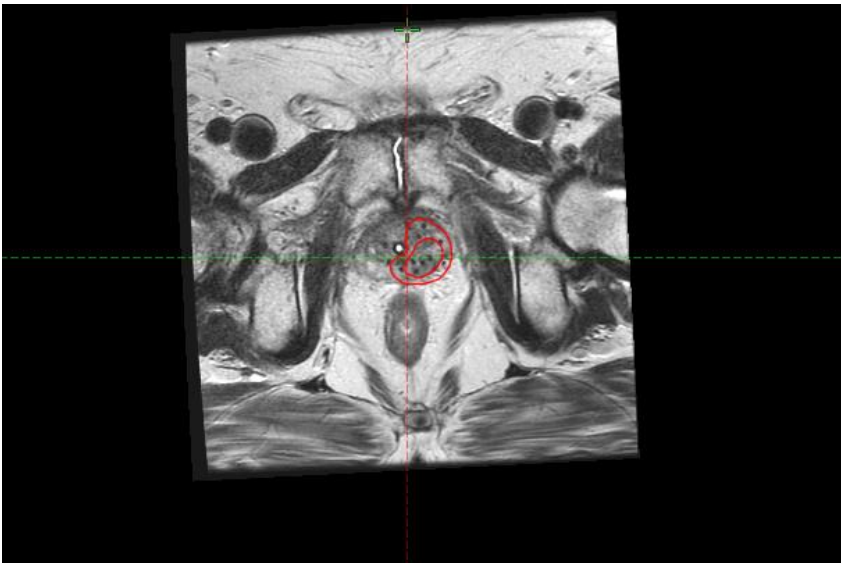


Figure 3 T2 MRI contours with inner red line is the GTV and the outer red line is the CTV

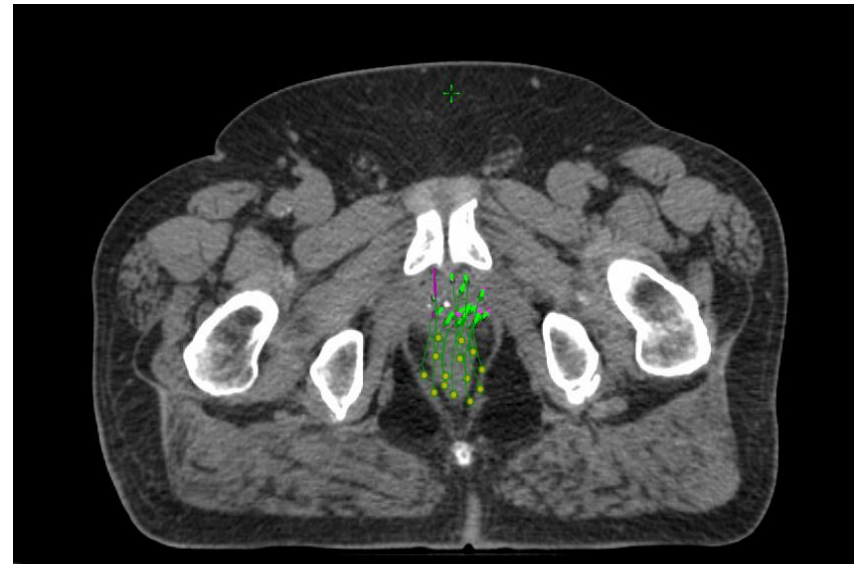


Figure 4 catheter reconstruction on CT

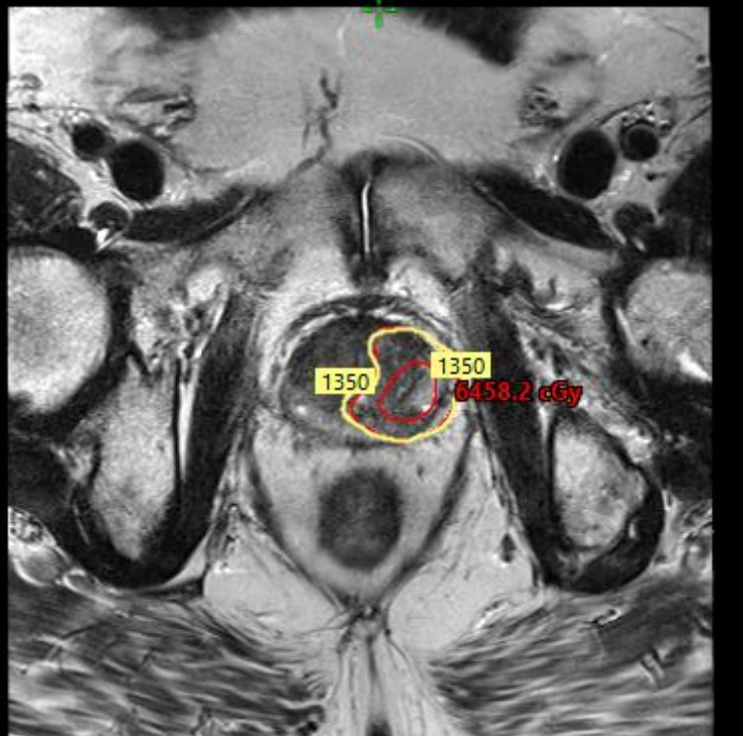
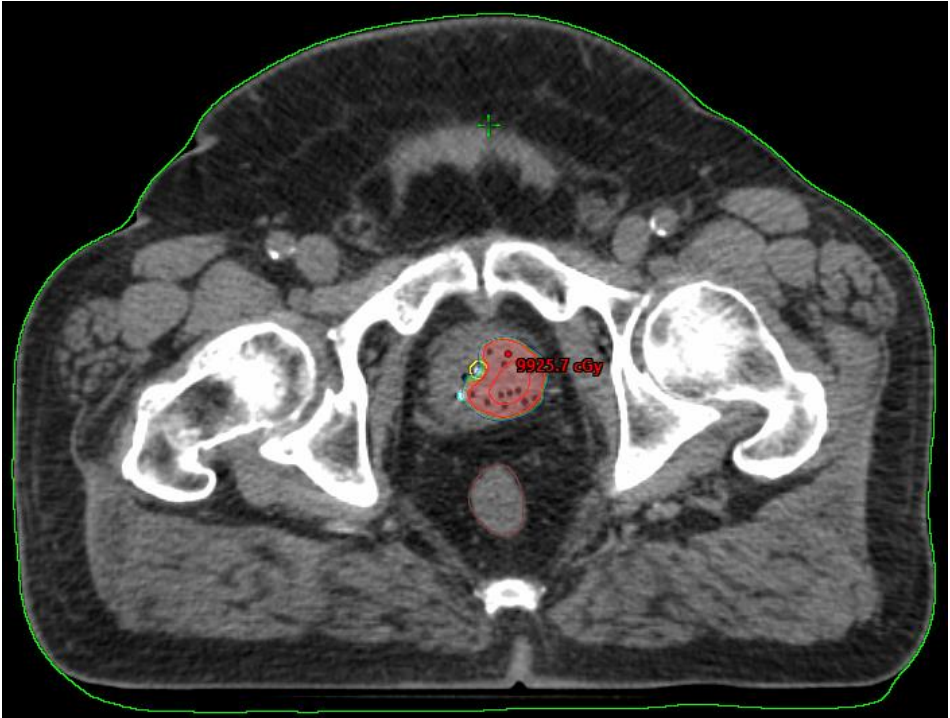


Figure 1 shows the planning MRI images of the 100% isodose line(yellow) covering the CTV(outer red line)

Figure 2 shows the planning CT images showing dose color wash for the prescription dose(13.5Gy)



Post-treatment follow up

- ✓ Patient is 5 months post treatment with follow up PSA showing downtrend from PSA 4.15 to PSA 2.07
- ✓ Has mild dysuria and urgency. He is using 0.4 mg tamsulosin
- ✓ Has ED pre-RT baseline and uses Viagra with success

Discussion

Loco-regional Accounts for 50% of Clinical Recurrences after Definitive EBRT

N=2694 patients treated with EBRT

Biochemical Recurrence
n=609 (23%)

Clinical Recurrence
n=474
(18% of entire cohort)

Patterns of 1 st Clinical Failure				
	Low (n=34)	Intermed (n=173)	High (n=267)	Overall (n=474)
Local	25 (74%)	117 (68%)	120 (45%)	262 (55%)
Pelvic Nodes	0 (0%)	33 (19%)	68 (25%)	101 (21%)
Abdominal Nodes	2 (6%)	16 (9%)	25 (9%)	43 (9%)
Thoracic Nodes	0 (0%)	7 (4%)	3 (1%)	10 (2%)
Bones	8 (24%)	43 (25%)	108 (40%)	159 (34%)
Viscera	0 (0%)	1 (<1%)	8 (3%)	9 (2%)

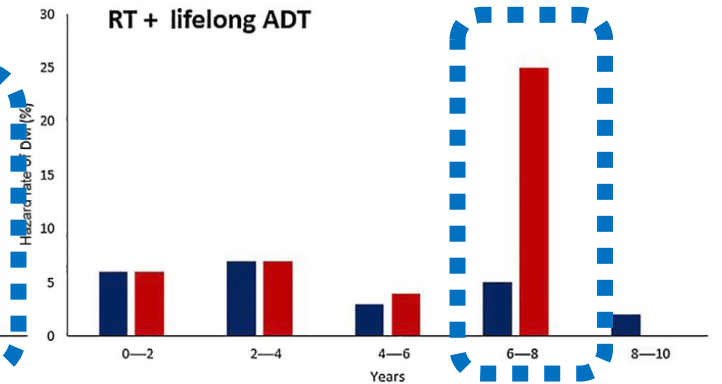
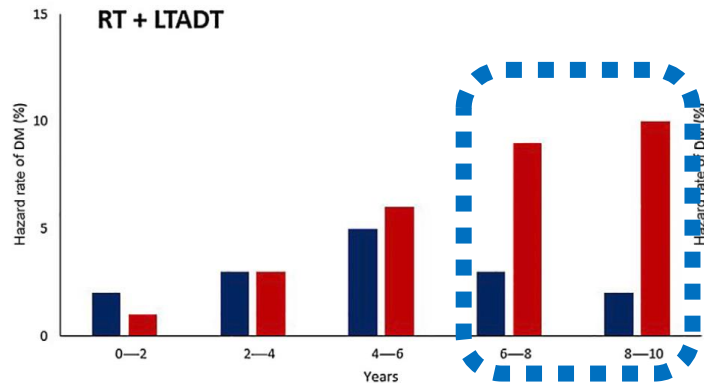
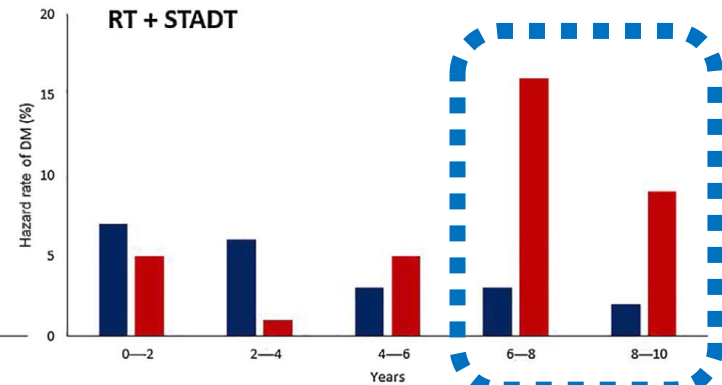
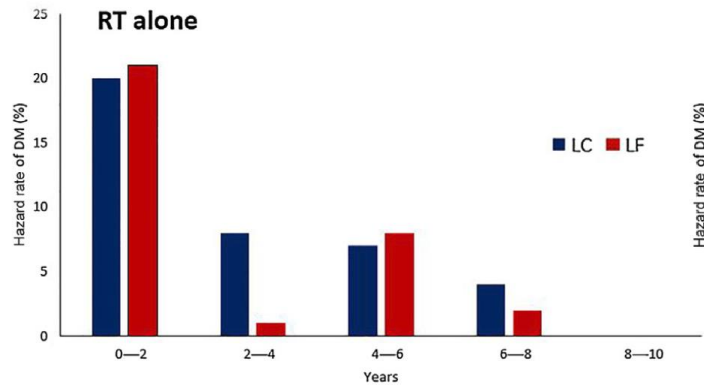
Zumsteg, J Urol, 2015

Slide courtesy of Solanki, pASTRO, 2020

Local recurrence may lead to subsequent Metastatic Disease

Individual Patient-level
Meta-analysis of 6
trials:

Trial
RTG 8531
RTG 8610
RTG 9202
EORTC 22863
EORTC 22961
EORTC 22991



Kishan, Eur Urol, 2019

Slide courtesy of Solanki, pASTRO, 2020

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

Table 1 – Summary of patient and treatment characteristics for local salvage modalities

	Age (yr)	Whole-gland salvage (%)	Biopsy-proven recurrence (%)	Presalvage PSA (ng/mL)	Perisalvage ADT use (%)	Interval from initial treatment to recurrence or salvage (mo)	Median follow-up (mo)	Number of studies (n)	Number of patients (n)
RP	65	100	99	6.0	16	50	47	52	2686
Cryotherapy	66	93	99	5.8	35	63	32	32	5153
HIFU	69	86	100	5.0	18	63	33	20	1783
SBRT	72	61	81	4.0	37	89	26	8	261
HDR	71	85	94	4.5	43	61	40	16	586
LDR	69	92	95	5.5	37	67	52	32	853

ADT = androgen deprivation therapy; HDR = high-dose-rate brachytherapy; HIFU = high-intensity focused ultrasound; LDR = low-dose-rate brachytherapy; PSA = prostate-specific antigen; RP = radical prostatectomy; SBRT = stereotactic body radiotherapy.

Majority of studies do whole gland salvage, increasing trend with SBRT and HDR to focal gland therapy

Table 3 – Covariate-adjusted meta-regression comparing efficacy and toxicity between salvage modalities and radical prostatectomy

	2-yr RFS	5-yr RFS	Severe GU toxicity	Severe GI toxicity
Radical prostatectomy				
Adjusted percent ^a (95% CI)	72% (66–78%)	53% (46%–59%)	21% (16%–26%)	1.5% (0.4%–3.2%)
Odds ratio (95% CI)	1.0	1.0	NA	NA
p value	Reference	Reference	Reference	Reference
R ² (%)	0.0	0.0	0.0	0.0
Cryotherapy				
Adjusted percent ^a (95% CI)	66% (59–72%)	57% (49–65%)	15% (8–23%)	0.9% (0.3–1.8%)
Odds ratio (95% CI)	0.74 (0.49–1.12)	1.20 (0.80–1.79)	NA	NA
p value	0.2	0.4	0.2	0.5
R ² (%)	25	0.0	8.2	27
HIFU				
Adjusted percent ^a (95% CI)	52% (45%–59%)	46% (37%–55%)	23% (17%–30%)	0.8% (0.1%–2.1%)
Odds ratio (95% CI)	0.42 (0.28–0.64)	0.76 (0.48–1.21)	NA	NA
p value	<0.001	0.2	0.5	0.4
R ² (%)	0.0	41	15	22
SBRT				
Adjusted percent ^a (95% CI)	58% (46–69%)	56% (37–73%)	5.6% (1.4–12%)	0.0% (0.0–1.2%)
Odds ratio (95% CI)	0.52 (0.30–0.93)	1.13 (0.50–2.58)	NA	NA
p value	0.03	0.8	<0.001	0.07
R ² (%)	55	4.2	0.00	0.0
HDR				
Adjusted percent ^a (95% CI)	77% (69–83%)	58% (52–64%)	9.6% (6.0–13.9%)	0.0% (0.0–0.3%)
Odds ratio (95% CI)	1.26 (0.77–2.09)	1.25 (0.88–1.78)	NA	NA
p value	0.4	0.2	0.002	0.003
R ² (%)	0.0	91	0.0	0.0
LDR				
Adjusted percent ^a (95% CI)	79% (72–85%)	53% (43–63%)	9.1% (5.2–14%)	2.1% (0.6–4.0%)
Odds ratio (95% CI)	1.49 (0.89–2.50)	1.02 (0.63–1.67)	–	–
p value	0.13	0.9	0.001	0.6
R ² (%)	4.3	5.2	12	20%

CI = confidence interval; GI = gastrointestinal; GU = genitourinary; HDR = high-dose-rate brachytherapy; HIFU = high-intensity focused ultrasound; LDR = low-dose-rate brachytherapy; NA = not available; RFS = recurrence-free survival; SBRT = stereotactic body radiotherapy.

Significant p-values after Bonferroni correction appear in bold.

^a Back-transformed regression coefficients for ease of interpretation.

SBRT and HDR seem to have the best outcomes with acceptable toxicity
 HDR studies were mainly whole gland compared to our patient where focal therapy was done

Outcomes with Salvage LDR and HDR

Study	Design	N	Local Therapy	Dose/Fx	Median f/u (months)	Biochemical Control	Distant Metastasis
Mount Sinai Burri, IJROBP, 2010	Retrospective	37	LDR	110 Gy Pd-103	86	5 y FFBF 65%	5 y MFS 94%
Princeton Baumann, Brachytherapy, 2017	Retrospective	33	LDR/HDR	Med. 100 Gy Pd-103 Med. 30 Gy in 6 fx	61	5 y PSA-RFS 79%	5 y MFS 93%
Spanish Multi-institutional Lopez, Radiother Oncol, 2019	Retrospective	119	LDR/HDR	Mean 145 Gy 32 Gy in 2-4 fx	52	5 y PSA-RFS 71%	~80-85% without DM
MSKCC retrospective Kollmeier, Brachytherapy, 2017	Retrospective	98	LDR/HDR	Mostly 125 Gy Pd-103 Mostly 32 Gy in 4 fx	31	5 y PSA-RFS ~55%	3 y MFS 79%
UCSF Boreta, pASTRO, 2019	Retrospective	139	HDR	32 Gy in 4 fx 36 Gy in 6 fx	61	5 y bNED 42%	Not reported
Netherlands Juliet Van Son, IJROBP, 2020	Retrospective	50	HDR	19 Gy x 1 fx	31	2.5 y bPFS: 51%	2.5 y DMFS 75%
Leeds Slevin, CTRO, 2020	Retrospective	43	HDR	19 Gy x 1 fx	26	2 y bPFS 71%	2 y FFDM >90%
Mt. Vernon Chitmanee, Clin Oncol, 2020	Retrospective	50	HDR	19 Gy x 1 fx	21	2 y bPFS 63%	2 y FFDM >90%
MSKCC phase II Yamada, Brachytherapy, 2014	Prospective	42	HDR	32 Gy in 4 fx	36	5 y PSA-RFS 69%	5 y MFS 81.5%
Sunnybrook Murgic, IJROBP, 2018	Prospective	15	HDR	27 Gy in 2 fx	36	3 y PSA-RFS 61%	3 y FFDM 100%
RTOG 0526 Crook, pASTRO, 2020	Prospective	100	LDR	140 Gy I-125 120 Gy Pd-103		pASTRO 2020	

Most series suggest 5-y PSA-RFS: ~50-60% and 5-y MFS: ~75-90%

Slide courtesy of Solanki, pASTRO, 2020

Emerging Data for Salvage SBRT

Study	Design	N	Local therapy	Dose/Fx	Median f/u (months)	Biochemical Control	Distant Metastasis
European Institute of Oncology Jereczek-Fossa, BJR, 2018	Retrospective	64	SBRT	Median 30 Gy/5	26	2 y bRFS 40%	2 y FFDM ~81%
Genesis Health Partners Fuller, IJROBP, 2019	Retrospective	50	SBRT	34 Gy/5	44	5 y bPFS 50%	5 y FFDM ~90%
GETUG Multi-institutional Pasquier, IJROBP, 2019	Retrospective	100	SBRT	Median 36 Gy/6	29	3 y bPFS 50%	3 y FFDM 93%
Humanitas University D'Agostino, IJROBP, 2019	Retrospective	33	SBRT	Median 25 Gy/5	33	2 y bRFS 42%	Not Reported
Northern Sydney Cancer Center Bergamin, IJROBP, 2020	Prospective	25	SBRT	36-38 Gy/6	25	2 y FFBF 80%	Not Reported

- Series suggest salvage SBRT has similar efficacy to salvage brachytherapy
- GETUG-AFU 31 (NCT03438552): Ongoing phase I/II trial of salvage SBRT powered for toxicity

Slide courtesy of Solanki, pASTRO, 2020

Unanswered Questions Remain

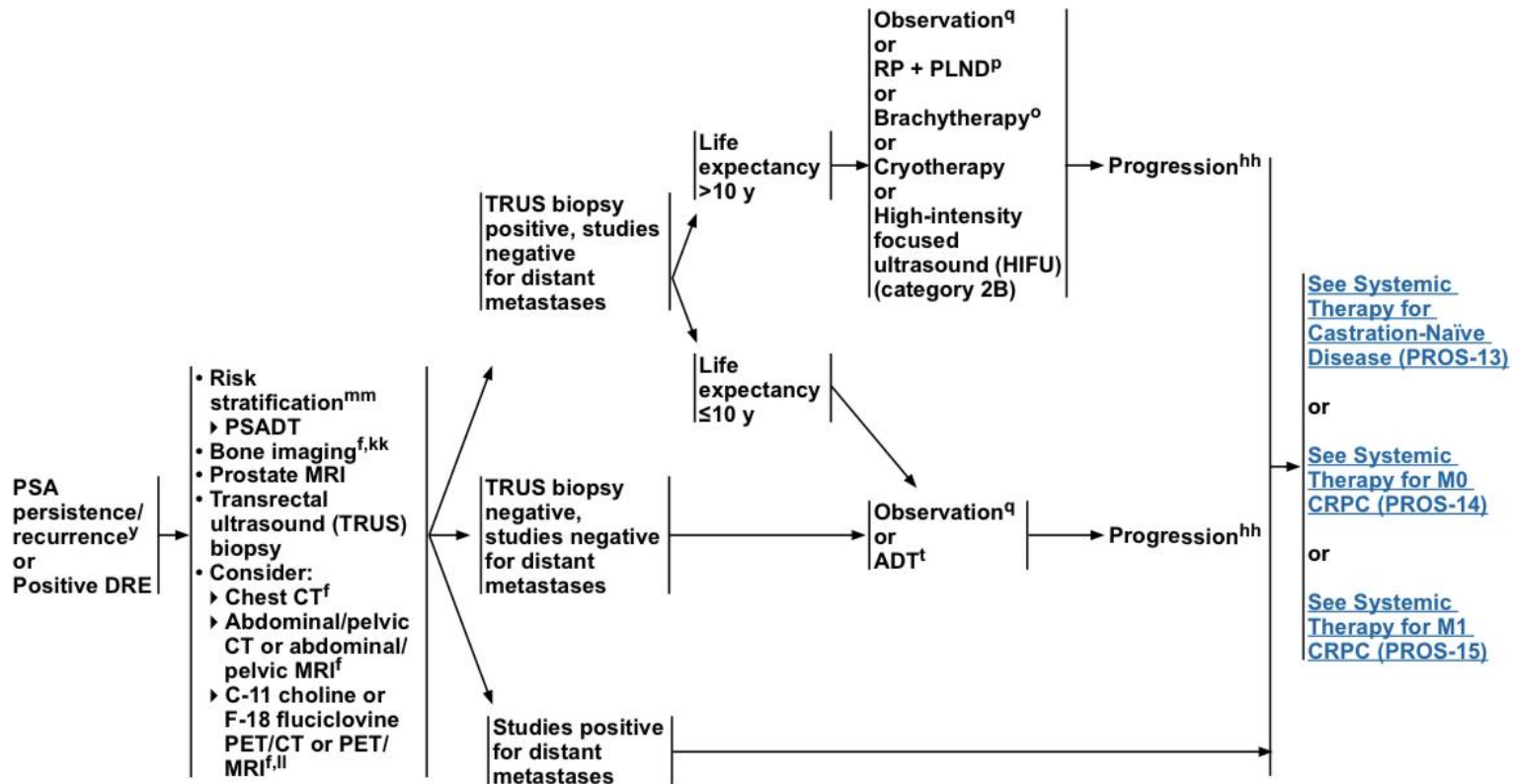
- Patient selection



NCCN Guidelines Version 2.2021
Prostate Cancer

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RADIATION THERAPY RECURRENCE



Initial Risk Group and Type of RT?

Study	Local Therapy	Initial Risk Group	Type of Initial RT
RTOG 0526	LDR	Low or Intermediate Risk	EBRT
Spanish Multi-institutional	LDR/ HDR	All risk Groups (~1/3 High Risk; 20% GG 4-5)	EBRT, LDR
MSKCC Retrospective	LDR/ HDR	All Risk Groups	EBRT, Brachytherapy
MSKCC prospective	HDR	All risk Groups	EBRT
UCSF	HDR	All Risk Groups	EBRT, Protons, SBRT, HDR, LDR
Genesis Health Partners	SBRT	Not reported	EBRT, Brachytherapy, SBRT
GETUG Multi-institutional	SBRT	All Risk Groups (42% High Risk)	EBRT +/- BT
Netherlands	HDR	All risk Groups (26% cT3a, 12% GG 4-5)	EBRT, LDR
Mount Sinai	LDR	All Risk Groups (24% high risk)	EBRT, LDR
Princeton	LDR/ HDR	All Risk Groups (55% High risk, 20% T3, 20% GG 4-5)	EBRT
Northern Sydney Cancer Center	SBRT	All Risk Groups (44% High risk)	EBRT, EBRT+HDR, LDR

- **Most series include High Risk patients (~25-40%)**
- **Mostly EBRT, but series also include prior brachytherapy and SBRT**

Recurrent Disease Characteristics?

Study	Recurrent Disease PSA	Recurrent T-classification	Time from prior RT
RTOG 0526	PSA < 10	No extraprostatic disease	Minimum 2.5 y
Spanish Multi-institutional	No cutoff (Max 16.7, median 4)	No extraprostatic disease	No minimum
MSKCC Retrospective	No cutoff (Max 59, median 3.7)	33% MRI ECE, 11% MRI SVI	Minimum 1 y
MSKCC Prospective	PSA ≤10	No Extraprostatic disease	Not reported
UCSF	No cutoff (Median 4.6)	cT3a: 19%, cT3b: 26%	No minimum
Genesis Health Partners	No cutoff (Max 48, median 4)	Up to T3b	Minimum 2 y
GETUG Multi-institutional	No cutoff (Max 38, median 4.3)	No ECE or SVI	Minimum 2 y
Netherlands	No cutoff (Max 39, median 17)	6% MRI ECE, 28% MRI SVI	Minimum 2 y
Mount Sinai	No cutoff (75% < 10)	Not reported	Not reported
Princeton	No cutoff (88% < 10)	No ECE or SVI	Minimum 1.5 y
Northern Sydney Cancer Center	PSA < 15	MRI ≤T2a	Minimum 4 y

- Most had no strict cutoff
 - Mostly PSAs < 10
- ECE or SVI included in several series
- Most ~≥2 years from prior RT in most series

Prognostic Features for Disease Control and Toxicity

Study	Local Therapy	Poor Prognostic Features for Disease Control	Prognostic Features for Toxicity
RTOG 0526	LDR	pASTRO 2020	Higher V100
Spanish Multi-institutional	LDR & HDR	Higher nadir PSA after salvage Disease-free interval <30 months	None reported
MSKCC Retrospective	LDR & HDR	Salvage PSADT <12 months	None reported
MSKCC prospective	HDR	None	Baseline urinary function predicted for G2 but not G3
UCSF	HDR	T3b Disease-free interval <4 years >35% cores involved & GG 4-5	None reported
Genesis Health Partners	SBRT	Salvage PSA > 6.92 ng/ml	Modality – prior brachy or SBRT had higher ≥G3+ toxicity
GETUG Multi-institutional	SBRT	Higher initial risk group Shorter disease-free interval Lower BED of salvage SBRT	BED associated with ≥G1 toxicity
Netherlands	HDR	Higher PSA (≥10), PSADT ≤9 MRI ≥T3 bigger size of CTV	None reported
Mount Sinai	LDR	Salvage PSA > 6	PLND prior to salvage associated w/ ≥G2 toxicity
Princeton	LDR & HDR	Older age at diagnosis & Older age at salvage Higher PSA nadir after initial RT Higher presalvage PSA	None reported

- Higher PSA nadir and presalvage level, shorter PSADT, shorter disease-free interval, and ECE/SVI lead to worse prognosis
- No consistent predictors of toxicity

Unanswered Questions Remain

- Patient selection
 - NCCN
 - Most published series are relatively inclusive
- Prognostic features for disease control and toxicity
- Role of short course of hormonal therapy in the setting of salvage radiotherapy
- **Role of focal therapy**

Summary

- Locally radiorecurrent prostate cancer is a common and clinically meaningful disease state
- Local therapy using brachytherapy or SBRT can salvage ~60% of patients with local radiorecurrence with an ~5-15% risk of severe toxicity
- Unanswered questions remain regarding patient selection and optimal treatment

References

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