THE BRISTOL CANCER INSTITUTE

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Salvage HDR Brachytherapy

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Disclosures

- Still No financial disclosures!

- Limited personal experience of HDR Brachy as salvage option

Background

- 20%-50% of patients develop biochemical failure within 10 years even with modern techniques and dose-escalation
  - Zelefsky etal, JCO 2005
  - Kuban et al, IJROBP 2003
- Post-EBRT prostate biopsies show that a significant proportion of these failures are due to local residual or recurrent disease.
- Out of patients who biochemically relapse: 25% are observed, 70% are offered ADT. Fewer than 5% undergo potentially curative local salvage.
  - Agarwal PK et al, Cancer 2008
  - Tran et al, Urol Oncol 2014
- Although a conservative approach may well be appropriate for many individuals, selected patients could benefit from retreatment with curative intent.

Salvage options

- The local salvage options include
- Salvage prostatectomy
- Salvage brachytherapy
  - Focal or whole gland
  - LDR or HDR
- Cryotherapy
- High-intensity focused ultrasound (HIFU)
- Stereotactic body radiotherapy (SBRT)
- No randomised trials comparing these options

Patient Selection

- **Patient factors**:
  - Life expectancy
  - Comorbidities

- **Tumour factors**: Local recurrence vs. Systemic spread
  - PSA nadir ≥2 ng/mL,
  - PSA doubling time (DT)≤6 months,
  - Interval to biochemical failure ≤ 18 months

  are all strongly associated with occurrence of distant metastasis
    - Kapadia et al, Cancer 2012
    - Shilkrut et al, IJROBP 2013

- **Risk-benefit ratio**

Patient Selection

Table 1 Selection Criteria and Prognostic Factors for Salvage Treatment Postradiation Failure

Study	Patients Characteristics	Tumor Characteristics
Nguyen (2007)[70]	Life expectancy $\geq$ 10 y	T1c-T2a Gleason score $\leq$ 6, PSA $<$ 10 ng/mL PSA velocity $<$ 2 ng/mL/y Interval to BF $>$ 3 y PSA-DT $>$ 12 mo s-PSA $<$ 10 ng/mL
Salvage brachytherapy		
Beyer[60]	Life expectancy $>$ 5-10 y	Interval to BF $>$ 2 y PSA $<$ 10 ng/mL PSA-DT $>$ 6-9 mo
Kaljouw et al[110](Uro-GEC Delphy consensus)	Life expectancy $>$ 5 y ECOG 0-1 IPSS $\leq$ 15	$\leq$T3b (Initial or salvage or both) Gleason Score $<$ 8 PSA-DT $>$ 6 mo s-PSA $\leq$ 10 ng/mL

- *Tetreault-Laflamme et al, Semin Radiat Oncol 2017*
- *Nguyen et al, Cancer 2007*
- *Beyer et al, Oncology 2004*
- *Kaljouw et al, Radiother Oncol 2015*

Patient selection

Table 4 Recommended Selection Criteria for Salvage Local Therapy Postradiation Failure

Patients characteristics
Life expectancy $\geq$ 10 y
Tumor characteristics
Biopsy-proven local disease with minimal or no radiation effect
Absence of systemic disease on imaging
PSA-DT $>$ 6 mo (preferably $>$ 12 mo)
Gleason score preferably $<$ 7 (higher Gleason acceptable if all other criteria met)
PSA at salvage $<$ 10 ng/mL
Interval to radiation $>$ 3 y

- *Tetreault-Laflamme et al, Semin Radiat Oncol 2017*

Patterns of local relpase

- Salvage RP has taught us much about the pattern of local recurrence in the prostate

- The pattern of recurrence seen in salvage prostatectomies (n=50):
  - 74% of cases had bilateral tumour,
  - 54% had T3a-b disease,
  - 74% had tumour within 5 mm of the urethra.

  – Leibovici et al, J Urol 2012

- Radiotherapy failures tend to occur at the site of the previous dominant lesion rather than being diffusely infiltrating throughout the gland.

  – Pucar et al, IJROBP 2007

Work-up

- Multiparametric MRI (DCE sequences) followed by targeted/ fusion biopsies
  - Biopsy review by an expert genitourinary (GU) pathologist is essential
  - Residual tumour with minimal or no radiation change must be demonstrated on histopathology before considering any local salvage option
- Staging: Standard: CT and BS
  - If expertise and facility available WB-MRI/PSMA PET

Salvage BRT: Considerations

- Local recurrence
  - Is it radioresistant?
  - Is it due to insufficient dose?
- Any patient being considered for salvage brachytherapy should have no or minimal (grade 1) side effects from their initial EBRT.
- Increased risk of side-effects
  - Acute s/e take up to 24m to return to baseline
  - More frequent late toxicities
  - Gr 3 GU – 10-25%
  - Gr 3-4 rectal ulcers – 2-6%
- Rectal spacer

Dosimetry

Table 2 Total physical prescription doses and normal tissue constraints (as percent of the prescribed reference dose) of various salvage HDR protocols

Study	PTV	Rectum	Bladder	Urethra	D90
Tharp et al., 2008 [8]	6.0 Gy × 4 7.0 Gy × 3 7.0 Gy × 6 9.0 Gy × 2	Dmax < 65–70%	Dmax < 75–80%	Dmax < 105%	N. R.
Yamada et al., 2014 [9]	8.0 Gy × 4	Dmax < 100%	N. R.	Dmax < 120%	>95%
Chen et al., 2013 [10]	6.0 Gy × 6	D1 cm^3 ≤ 75%	D1 cm^3 ≤ 75%	D1 cm^3 ≤ 125%	>100%
Kukieka et al., 2014 [11]	10.0 Gy × 3	Dmax < 80%	N. R.	Dmax < 120%	>95%
Wojcieszek et al., 2016 [12]	10.0 Gy × 3	D10 cm^3 ≤ 70%	D10 cm^3 ≤ 70%	D10 cm^3 ≤ 120%	>100%

D90 the dose receiving at least 90% of the prostate, *Dmax* maximum dose, *D1 cm^3* maximum dose to the most exposed 1 cm^3 of the organ, *D10 cm^3* dose delivered to 10 cm^3 of the organ, *N.R.* not reported

- Dose constraints
  - Same as primary treatment?

PTV: D90 ≥ 19 Gy
V100 ≥ 95%

Urethra: D30< 20.8 Gy
D10 < 22 Gy
V150=0 cc

Rectum: D2cm^3 ≤ 15Gy
V100=0 cc

Case series

Table 2 Salvage Brachytherapy Series

Studies	Patients	Brachytherapy Type	Median Follow-Up (Mo)	BCR-Free Survival (Interval)	CSS (Y)
Aaronson et al[73]	24	LDR	30	86% (2.5 y)	96% (2.5 y)
Burri et al[61]	37	LDR	86	65% (5 y) 54% (10 y)	96% (10 y)
Grado et al[63]	49	LDR	64	34% (5 y)	79% (5 y)
Hsu et al[79]	15	LDR (MRI-planned partial salvage)	24	71.4% (3 y)	
Lee 2008[65]	21	LDR	36	38% (5 y)	
Moman et al[74]	31	LDR	108	20% (5 y)	65% (6 y)
Nguyen et al[70]	25	LDR (MRI-guided BT)	47	70% (4 y)	
Peters et al[111]	20	LDR (focal salvage)	36	6 Events	
Rose et al[69]	18	LDR (3 focal salvage)	31.5	78% (3 y)	
Vargas et al[66]	69	LDR	60	73.8% non-CRPC, 22% CRPR (5 y)	95.6% (5 y)
Henriquez et al[64]	56	37 LDR/19 HDR	48	77% (5 y)	
Chen et al[62]/Lee et al[80]	52	HDR	60	51% (5 y)	
Jo et al[81]	11	HDR	29	64% (2 y)	
Tharp et al[82]	7	HDR	58	71%	71%
Yamada et al[67]	42	HDR	36	68.5% (5 y)	90.3% (5 y)

Abbreviations: BCR, BCR using Phoenix definition; CRPC, castrate-resistant prostate cancer; MRI-guided BT, magnetic resonance guided brachytherapy.

Case series

Author	n	Med FU (m)	BCR free survival	Toxicity	Comments
Lee et al, IJROBP 2007	21	19	@ 2yr – 89%	14% Gr3 GU, no Gr3 GI tox	36Gy/6#
*Tharp et al, Brachytherapy 2008	7	58	71%	28% Gr3 GU No Gr3 GI tox	18-42Gy/2-6#
*Lyczek et al, J Contemp Brachy 2009	115	60	46% - GS 6 18% - GS ≥6	1.7% urethral fistulas 1.7% urinary incontinence 3.4% bladder outlet obstruction	30Gy/3#, 3 implants, 3 wkly
Pellizzon et al, ASCO abstract 2009	17	47	70.5%	Strictures-5.9% Gr3 GI – 5.9%	34-36Gy/4#
*Jo Y et al, BJU Int 2011	11	29	@2yr – 67%	No Gr3 GU/GI tox	22Gy/2#
Oliai et al, IJROBP, 2013 Prospective	22	45	@2yr-95.5%	18% hematuria 32% urethral strictures	36Gy/6#, 2 implants
*Chen et al, IJROBP 2013	52	59.6	@5yr – 51%	Gr2 GU-54% Gr3 GU -2% Gr2 GI<4% No Gr3 GI tox Gr 3 sexual dysfn-6%	36Gy/6#, 2 implants, 1 wk apart DC were PTV D_{90} ≥ 100%, bladder $V_{75\%}$ < 1 cc , rectum $V_{75\%}$ < 1 cc, urethra $V_{125\%}$ < 1 cc.

* Patients had brachytherapy +/- EBRT as primary treatment

Case series

Author	n	Med FU	BCR free survival	Toxicity	Comments
Yamada et al, Brachytherapy 2014 (Prospective)	42	36m	@5yr – 68.5%	3pts – stricture 1pt- incontinence No Gr3 GI tox 48% Gr 2 GU, 14% Gr 2 GI 8.8% Gr 3 GU	32Gy/4#, 1 implant over 30 hrs 43% had NADT (3m)
Guerif et al, Brachytherapy 2014	15	11m	1 pt had BCR	No Gr3 GU/GI tox	
*Henriquez et al, Radiat Oncol 2014	19	48m	@5yr-77%	21% Gr 3 GU 2% Gr 3 GI	17-34Gy/1-4#, 1-3 Implants Pts had ADT (NADT+AADT) 29% were high risk
Kukielka et al, Strahlenther Onkol 2014	25	13m	@2yr – 74%	No Gr3 GU/GI tox 9% Gr 2 nocturia 4.5% Gr 2 obstruction 4.5% Gr 2 frequency	BRT+ Hyperthermia
*Wojcieszek et al., Radiother Oncol 2016	83	41m	@3yr-76% @5yr-67%	39% Gr 2 GU 13% Gr 3 GU 6% Gr 1 GI	30Gy/3#, 3 implants
Mbeutcha et al Radiat Oncol 2017	10	22m	@19.5m – 44.4%	10% Gr3 GU, no Gr3 GI tox	N=28 (10/18: HDR/ SBRT) 35Gy/5#/ 5d CTV: V100 - ≥95%; V150 <30%, and V200 <12%. Urethra: V115 <1% Rectum: V80 <1%.
Baumann et al, Brachytherapy 2017	31	61	@5yr-79% 100% in those with HDR	No acute Gr 3 tox Late: Gr 2 GU-18% Gr 3 GU-12% No Gr3 GI tox	25-LDR, 8-HDR, 55% were High risk 30GY/6#, 4 wks with 4-6m of ADT (NADT+AADT) V95 – 100% Urethra V125 – 0

* Patients had brachytherapy +/- EBRT as primary treatment

Salvage HDR brachytherapy – Bristol Experience

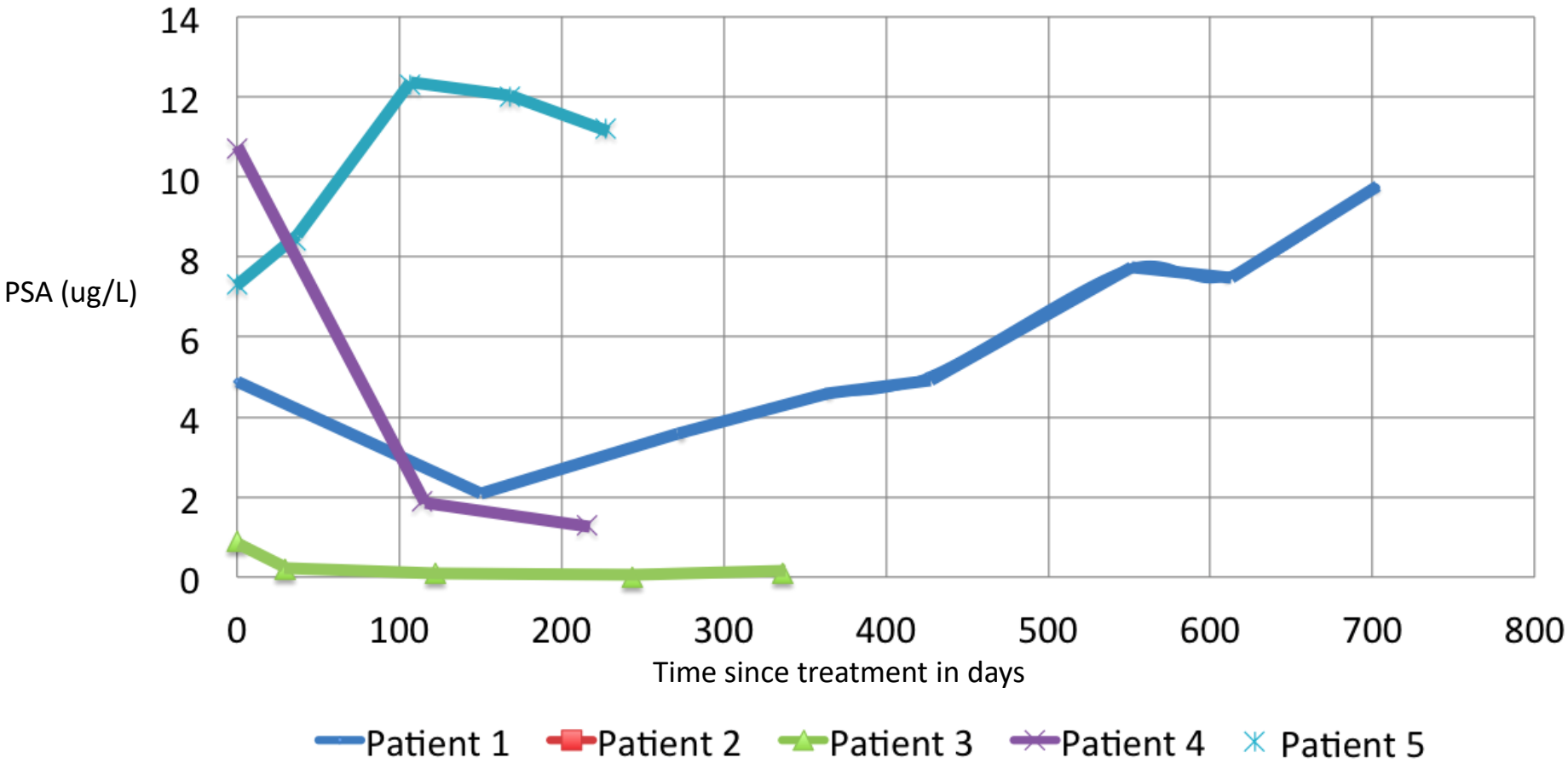
March 2018

5 Patients with >6month F/U

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	Initial	**Salvage**	**Initial**	**Salvage**	**Initial**	**Salvage**	**Initial**	**Salvage**	**Initial**	**Salvage**
Age	57	61	68	72	63	69	59	75	66	70
PSA	18	8.0	not known	1.8 (on adjuvant ADT)	17.5	0.6 (on ADT for biochemical relapse)	71	10.7	7.4	8.2
Gleason score	3+4	-	3+4	-	3+3	-	3+3	3+4	3+4	-
Disease location	-	left sided	-	anterior	-	right sided	-	Multifocal, bilateral	Multifocal	Multifocal, bilateral
Stage (MRI)	T3aN0M0	No extraprostatic disease	T3aN0M0	No extraprostatic disease	T2aN0M0	No extraprostatic disease	-	T2cN0M0 Left >Right	T2cN0M0	No features of focal tumour ('post radiotherapy gland')
Imaging pre salvage	^{11C}Choline-PET		^{11C}Choline-PET		CT Chest, abdomen, pelvis with contrast; ^{99m}Tc whole body bone scan		CT Chest, abdomen, pelvis with contrast; ^{99m}Tc whole body bone scan		CT Chest, abdomen, pelvis with contrast; ^{99m}Tc whole body bone scan	

- All staged with Prostate MRI; 4/5 (80%) of these were pre-biopsy
- Choice of staging imaging depended on availability and referring centre standard practice

PSA Follow up



Follow up - Toxicity

- All successful TWOC within 24 hours of treatment, no re-catheterisations
- Initial increase in urinary frequency observed in all patients
- Urinary frequency/urgency returned to baseline by 8 weeks for 3/5 patients (Patients 2,3,4)
- Patient 1 had ongoing grade 1 GU toxicity at 1 year
- Patient 5 – increase to Grade 2 frequency/dysuria/reduced flow over 6 months which has subsequently improved to grade 1, (total follow up 7.5 months to date)

- No bowel toxicity observed to date

- Low response rate to IIEF scores at follow up; ED present at baseline in 3/5 patients

HDR salvage following EBRT in Bristol

- Safety and tolerability appears favourable
- Caution with rectal dose exercised
- Patient characteristics vary hugely:
- 1/5 patients continues to experience increase in PSA
- Short follow up limits interpretation of efficacy

Focal salvage

Author	n	Med FU	Toxicity	Comments
Chung et al, Brachytherapy 2015	11	6m	No acute Gr 3 GU/GI tox	27Gy/2#, 1 wk

Conclusions:

Comparative outcomes of Salvage Therapy Options

Table 3 Outcomes from Different Salvage Procedures

Salvage Treatment	Oncologic Outcomes (5 Y-BCR-Free Survival)	GU Toxicity	GI Toxicity
Prostatectomy	37%-65%	Bladder neck stricture 15%-25% Urethral anastomotic leak 15% Incontinence 35%-65%	Rectal injuries 5%-10%
Brachytherapy	50% (34%-77%)	Acute irritative urinary symptoms Urethral stricture 10%-20%	Rectal ulcers or bleeding or fistulas 2%-6%
Cryotherapy	50% (23%-70%)	Incontinence 3%-19%	Chronic perineal pain 14% Rectal fistulas 2%
HIFU	45%-54%	Urethral stricture 20%-38% Incontinence 10%-40%	Rectal fistulas 0.5%-6%

Scope for ‘personalised treatment’…… euphuism for lack of evidence