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High dose rate brachytherapy boost for prostate cancer: Biochemical control and the impact of transurethral resection of the prostate and hydrogel spacer insertion on toxicity outcomes

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Introduction

The treatment options for men diagnosed with localised prostate cancer have continued to improve over time with relative efficacy seen with various regimes involving radical prostatectomy, external beam radiotherapy (EBRT) and/or brachytherapy[1,2]. Several reviews have also shown that the use of combination therapies such as low-dose (LDR) or high-dose-rate (HDR) brachytherapy and EBRT have not only allowed for the delivery of maximum radiation dose to cancerous tissues and minimized exposure to organs at risk but have translated into improved biochemical progression-free survival (bPFS) and metastasis-free survival (MFS)[3,4].

Whilst LDR brachytherapy has been the cornerstone for prostate BT in low-risk patients for many years, the use of HDR brachytherapy has been shown to be more common in prostate patients with reported intermediate to high-risk disease[4,5]. Data from several randomized control trials showed have not only validated the combined modality approach as being superior to EBRT alone, but shown better treatment responses and lower gastrointestinal toxicities.

With regard to the treatment dose prescription, HDR brachytherapy has been delivered as either monotherapy or as a boost and with varying degrees of fractionation[6]. Given the potential clinical advantages of delivering HDR brachytherapy boost (HDR-BT) we conducted a retrospective, single centre study examining the safety and effectiveness of HDR-BT combined with EBRT as measured by overall treatment toxicities and biochemical and clinical disease control rates in a series of prostate cancer patients presenting with intermediate and high-risk disease.

Methods

Study design

This retrospective case series examined the safety and effectiveness of HDR-BT combined with EBRT for intermediate and high-risk prostate cancer patients in Melbourne, Australia. The Institutional Research Review Committee granted ethics approval. The primary objective of this study was to report the efficacy of HDR-BT combined with EBRT [overall bPFS, local recurrence free survival (LRFS), MFS and overall survival (OS)], whilst secondary objectives were limited to acute and late genitourinary (GU) and gastrointestinal (GI) toxicities for the entire cohort as well as patients with or without prior mini transurethral resection of the prostate (TURP) or hydrogel spacer (HS) insertion.

Planning and treatment procedure

All men were prospectively followed from initial review. A mini TURP was performed preoperatively in patients with bladder outlet obstruction, confirmed by cystoscopy. The HDR was scheduled at least three months post mini TURP. The ADT was recommended for six months in patients with intermediate risk and for 24 months in high-risk disease. In patients who agreed to ADT, this was started at least three months before the commencement of radiotherapy.

Our HDR-BT using Iridium 192 was performed two weeks prior to EBRT. Patients were placed in the semi-lithotomy position under spinal anaesthesia. Three gold fiducial markers were inserted into the prostate to facilitate image guided radiation therapy (IGRT) for both HDR-BT and EBRT. An average of 15 HDR catheters (OncoSmart ProGuide needles, Nucletron Pty Ltd) were inserted into the prostate transperineally using a template technique (5f prostate stepper template, Nucletron Pty Ltd) under transrectal ultrasound guidance. For patients treated from December 2013 (n= 30), polyethylene-glycol HS gel (SpaceOAR™, Augmenix, Waltham, MA, USA) was injected to displace the anterior rectal wall posteriorly from the prostate once all needles were inserted. Under flexible cystoscopy guidance to ensure the vesico-ureteric junction was not compromised, all needles were advanced 2.0 cm into the bladder to account for caudal displacement resulting from perineal oedema.

A computed tomography (CT) scan was acquired for planning and imported into Oncentra® (Elekta Pty Ltd) treatment planning system. The brachytherapy clinical tumour volume (CTV) was the prostate alone with a 2-3 mm margin to account for microscopic extension, except posteriorly where no margin was applied. The planning target volume (PTV) was the CTV. Dose

goals were PTV- V100> 95%, V150 < 35%, V200< 15%. The rectum was contoured as a whole solid structure beginning at 1.0cm above the most superior level of the PTV to the anorectal junction. The urethra was contoured using the outer surface of the Foley catheter. Rectal and urethral dose constraints were rectal V75 <1cc and urethral V125 <1cc. A total of 24 patients received an initial dose of 18Gy in 3 fractions from 2010-2011, with the remaining 71 patients receiving 16Gy in 2 fractions from 2012 onwards as per our departmental protocol.

Treatment was delivered using a single implant by a remote afterloading Ir192 source (Flexitron, Elekta Pty Ltd) with a minimum of 6 hours between fractions. Our treatment verification technique involved a digitally reconstructed radiograph (DRR) generated from the CT data set as the reference image for HDR catheter position relative to the fiducial markers. Prior to treatment delivery, a 2D image of the pelvis was acquired using a C-arm to assess HDR catheter position. A standard 2mm action threshold was applied.

Departmental bladder and rectal filling protocols were followed. The CTV was defined as the prostate and seminal vesicles. A margin of 7.0 mm in all directions except posteriorly, where it was 5mm was applied to the CTV to generate the PTV. Prescribed dose for EBRT was 50.4 Gy in 28 fractions. Treatment techniques utilised were intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT).

Evaluation of response: clinical endpoints

Overall survival and MFS were calculated from time of HDR-BT implant to date of last follow-up. The Phoenix definition (i.e. nadir + 2 ng/Ml) for bPFS was also used[7]. Acute and late toxicities focusing on GU and GI symptoms were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Toxicity assessments were performed weekly during treatment, then at two weeks and at three monthly intervals in the first year. Follow up with PSA continued thereafter at six monthly intervals. The cut off between acute and late toxicities was three months after the end of EBRT. Our analysis was based on the evaluation of the maximum toxicity score throughout treatment for each patient.

Statistical analysis

Descriptive statistics are presented as median and interquartile range (IQR:) for continuous variables and as frequency (percentage) for binary variables. The bPFS, LRFS, MFS and OS rates

were estimated using the Kaplan-Meier method. Estimates at specific time points with respective 95% confidence interval (95% CI) were also provided. The association between patient characteristics and disease-specific risk factors and bPFS, MFS and OS was determined using linear regression. Effect estimates were reported as mean difference (MD) with 95% CI. In all analyses, a value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed in R (version 3.1.1; R Development Core Team 2009) using standard and validated statistical procedures.

Results

A total of 95 patients with National Comprehensive Centre Network Prostate Cancer Guideline v.3.0[8] criteria-defined intermediate or high-risk prostate cancer were treated using initial HDR-BT followed by EBRT to the prostate and seminal vesicles between 2010 and 2017. All patients were free of distant metastases at the time of HDR-BT.

All patients were classifieds into low, intermediate or high (very high) risk based on the NCCN 2016 guidelines. A smaller subset also revealed 28 patients to be at very high risk. With a median age of 72.7 years (IQR: 52-83 years) and a median PSA level of 12.4 ng/ml (IQR: 3.2-47.0 ng/ml), the primary tumour staging was reported as T1 (19%), T2 (49%) and T3 (32%) using the Union for International Cancer Control TNM Classification 8th Edition[9]. Most patients (88%, n=84) were on ADT prior to therapy, whilst 15% (n=14) of patients had undergone prior TURP. All 30 patients underwent successful HS insertion with no postoperative complications reported. Table 1 shows patient demographics and disease-specific characteristics.

INSERT TABLE 1

Dosimetric values

The median prostate V100, V150 and V200 were 95.4% (IQR: 84.3-99%), 32.4% (IQR: 24.9-41.1%) and 12.1% (IQR: 9.6-15.7%). The median rectal V75 was 0.32 cc (IQR: 0.0-1.46cc) and median urethral V125 was 0.04 cc (IQR: 0.0-1cc). The use of HS was associated with a significantly reduced median rectal V75 of 0.0cc (IQR: 0-0.22) vs. 0.45cc (IQR: 0.0-1.46) (p<0.001).

Disease control

The median follow up was 58 months (IQR: 7-125 months), with only one patient lost to follow-up because of a move to another country. The 5-year bPFS, LRFS and MFS rate were 92% (95%CI 85-98%), 100% and 92% (95%CI 88-99%), respectively. At 5-years, the overall OS was 88% (95%CI 81-95%). Univariate regression revealed no statistical association between patient risk factors and time to relapse (all $p > 0.1$) (Table 2). Six patients experienced biochemical relapse at 35 months (IQR: 24-50 months), with the site of recurrence including either bone (n=3) or regional lymph node (n=3) metastases. All six patients underwent various treatment options (e.g. node dissection, stereotactic radiotherapy).

INSERT TABLE 2

Toxicity

The incidence of acute Grade 1 GU toxicity was 91.6%, with 1.1% developing Grade 2 GU toxicity (Table 3). No Grade 3 acute toxicity was seen. The incidence of late Grade 1, 2 and 3 GU toxicities were 44%, 6.3% and 5.3%, respectively. Grade 3 GU toxicities included urinary retention (n=4) secondary to urethral strictures, managed with optical urethotomy or TURP and severe haematuria (n=1). Undergoing prior TURP did not increase the risk of acute or late GU toxicity.

The incidence of acute Grade 1 GI toxicity was 25.3% with 1.1% developing Grade 2 GI toxicity. No acute Grade 3 GI toxicities were seen. The incidence of late Grade 1 GI toxicity was 5.3%. No late Grade 2 or 3 GI toxicities were observed. There was significantly less acute Grade 1 GI toxicity in the HS group compared to the non-HS group (13.3% vs. 30.8%; $p=0.05$). No patients in the HS group developed acute Grade 2 GI toxicity. There was also less late Grade 1 GU toxicity in the HS group compared to the non HS group but this was not statistically significant (0% vs. 7.7%; $p=0.11$).

INSERT TABLE 3

Discussion

The aim of this retrospective case series was to evaluate the safety and effectiveness of HDR-BT combined with EBRT as measured by biochemical and clinical disease control rates in 95 prostate cancer patients presenting with intermediate and high-risk disease. With a median follow-up rate of 58 months, the combined treatment modality resulted in 5-year bPFS and OS

rates of 92% and 88%, respectively. In addition, 32% of patients received hydrogel spacer to improve dosimetric outcomes and minimise adverse events.

Our results were consistent with other international studies that reported favourable biochemical control rates at 5-year median follow-up with hormonal therapy. In the study by Falk[10], 159 patients with localised prostate cancer (74.2% with high-risk disease) received various HDR-BT (6-14 Gy in 1-3 fractions) after EBRT (46 Gy in 23 fractions) that resulted in 5-year biochemical failure free survival (BFFS) and OS rates of 86.6% and 96.5%, with no significant differences seen between the boost doses. More so, patients receiving ADT exhibited a reduced BFFS and OS rates when compared to those not receiving ADT therapy. Vigneault[11] reported on the effects of various EBRT (36-44 Gy in 12-25 fractions) with HDR-BT (15-21 Gy in 1-3 fractions) regimes on 832 patients with localized prostate adenocarcinoma and showed BFFS rates for patients with intermediate and high risks cancers to be 94.6% and 93.5%, respectively (p=NS). In addition, patients receiving ADT (41.3% of the entire cohort) also showed a lower 5-year BFFS rate compared to those not receiving ADT therapy (90.5% vs. 96.5%, $p = 0.001$).

However, our biochemical control rate varied when compared to other Australian studies. In Yaxley[12], the authors reported on the effects of EBRT and HDR-BT with ADT in 507 men with prostate cancer. With a follow up rate of 10.3 years, the incidence of no biochemical evidence of disease (bNED) for men with intermediate and high risk disease were 93.3% and 74.2% respectively, at 5 years and 86.9% and 56.1% respectively, at 10 years. In Bece[13], the authors reported on disease outcomes and late urinary toxicities following EBRT and HDR-BT (17-19.5Gy in 2-3 fractions) with or without ADT in 180 patients with localised intermediate and high-risk prostate cancer. With a median follow up of 5.2 years, the 5-year freedom from failure was 93.7% for intermediate and 76% for high-risk patients. In our study, we did not find a correlation between T stage, ISUP grade, or NCCN risk groups. This is likely a consequence of our smaller patient cohort compared to the larger Australian studies.

In the study by Khor[14], the authors undertook a matched paired analysis and compared EBRT alone (74Gy in 37 fractions) versus EBRT (46Gy in 23 fractions) and HDR-BT (19.5Gy in 3 fractions) with or without ADT in 344 men with intermediate and high-risk prostate cancer. The 5 and 10 year freedom from biochemical failure was 70.9% and 32.8% respectively, in the EBRT cohort and 79.8% and 69.2% respectively, in the EBRT and HDR-BT cohort (p=0.0011). This statistically significant reduction in risk of biochemical failure was independent of ADT usage in

the EBRT and HDR-BT cohort, suggesting that this treatment approach was effective regardless of planned ADT usage.

However, we were mindful about making any real direct comparisons given the methodological variations seen across the brachytherapy literature. For example, many single centre studies reported on the use of either prostate versus pelvic EBRT; whereas heterogeneity was observed in the prescribed doses, both in terms of total dose and fraction and dose reporting. In addition, various disease risk stratification methods were employed (e.g. EBRT patients were stratified according to the NCCN system, whereas HDR-BT patients were stratified according to NCCN, risk factors and the American Joint Committee on Cancer (AJCC). Different prescribing patterns of ADT administration were also coupled with the use of different criteria to define biochemical failure.

Although we did not show a causal link between patients receiving ADT in the setting of EBRT plus HDR-BT nor collect data on ADT toxicities, the effect of ADT on biochemical control still remained uncertain within the literature. In a systematic review by Zaorsky[15], the authors reported on the theoretical benefits seen with HDR-BT and ADT in the treatment of extra prostatic disease amongst intermediate and high-risk patient. However, the authors were also cognizant that due to poor overall reporting of risk stratification of ADT use in most studies, it was almost impossible to integrate ADT findings into outcomes versus follow-up time plots. Therefore, making it difficult to discern the absolute benefits of HDR-BT or ADT alone.

Thiuthaneeswaran[16] observed that the role of ADT in the setting of HDR-BT remained poorly defined because of the various and conflicting results seen in recent published case series, but urged for its continuation in high-risk patients and in a case by case consideration for those patients with intermediate risk. However, Hannoun-Levi[1] recommended patients with high-intermediate risk prostate cancer should be offered the combination of EBRT (with or without) ADT plus brachytherapy boost (low or high dose rate) given the success of the RCT by Morris et al[17] which showed statistical benefit in low-dose rate brachytherapy boost compared to dose escalated external beam boost in 398 patients on ADT with intermediate and high-risk prostate cancer.

Late grade 3 GU toxicities were 5.3%, which fell within the ranges seen in a number of published reviews[2,6]. Similarly our urethral stricture rate of 4.2% was in keeping with a recent

review that reported crude rates from 0-14%[18]. However, our rates were significantly lower than other Australian studies[12,13,14], which we attribute to three strategies. First, the precise placement of a gold fiducial marker at the very apex of the prostate under transrectal ultrasound control significantly improved the accurate delineation of the prostatic apex on CT imaging. Second, we minimised any potential threat to caudal movement of the HDR catheters by imaging prior to each fraction and advancing the position of the HDR source within the catheters relative to the gold fiducial markers. Finally, 14 men (15%) underwent a mini TURP before receiving HDR-BT because of bladder outlet obstruction. This preventative strategy widened the prostatic urethral channel and reduced the risk of subsequent urethral strictures[12].

A prior mini TURP did not increase the risk of acute or late GU toxicity in the 14 patients who underwent the procedure. The rate of late Grade 1 or greater GU toxicity was higher in the TURP cohort compared to the non-TURP cohort but this was not significant (61.5% vs 41.5%, p=0.18). The rate of late Grade 3 GU toxicity was comparable between the two cohorts (7.7% vs 4.9%, p=0.67). No patient developed urethral necrosis or urinary incontinence after a mini TURP. This is consistent with contemporary reports from the HDR-BT literature where prior mini TURP was only associated with low increased GU toxicity[19,20]. A prior mini TURP did not result in a urinary incontinence rate of 18% as previously reported by Kollmeier et al.[21] The use of a prior mini TURP in LDR brachytherapy has also shown similar low GU toxicity with no urethral necrosis or urinary incontinence reported[22,23].

The use of HS was also safe with all patients successfully implanted with no postoperative complications reported. In addition, we reported less GI rectal toxicities in patients who underwent HS insertion. The HS group had significantly less acute toxicity. The rate of acute Grade 1 or greater GI toxicity was 13.3% in the HS group compared to 30.8% in the non-HS group (p=0.05). There was also a trend towards less late GI toxicity in the HS group. More so, early experiences with a rectal spacer in conjunction with LDR and HDR brachytherapy yielded other favourable clinical and dosimetric results[24,25]. In the study by Beydoun[24] in which five patients received I-125 seed brachytherapy implant and HS gel for T1 prostate adenocarcinoma, Grade 1 adverse effects were restricted to perineal pain and rectal discomfort. No Grade 2 rectal toxicities were reported. Yeh[25] reported toxicity outcomes in 326 patients with prostate cancer who underwent combined HDR-BT plus HS gel reported Grade 1 and Grade 2 toxicity rates of 37.4% and 2.8%, respectively. Late rectal grade 1 and 2 toxicities were reported to be 12.7 % and 1.4%.

Although a series of reviews[1,6,16] highlighted various safety and efficacy profiles of EBRT and HDR-BT combinations, there was still an overall decline in numbers of HDR-BT procedures performed throughout Australia. In the study by Ong[5], the authors evaluated the pattern of utilisation of HDR brachytherapy using the population-based Prostate Cancer Outcome Registry Victoria and government-based Medicare Benefit Schedule statistics. In 1806 men with prostate cancer who had definitive EBRT, only 124 (7%) had documented HDR-BT utilisation with EBRT. More so, there was a significant decline in numbers of HDR-BT performed throughout Australia from 313 cases in 2010 to 125 cases in 2015. Similarly, Orio[26] found in the United States that radiation oncology centres performing one case per week dropped from 6.7% to 1.5% and 4.5% to 2.7% in academic and non-academic practices, respectively. Explanations put forward for this were seen to be multifactorial, but were attributed to the use of various other EBRT techniques such as IMRT.

Study limitations

This study also had a number of limitations. In particular, we used a retrospective case series methodology despite all the patients were captured prospectively, which may have induced a potential patient selection bias. Secondly, our median follow-up of 58 months was potentially insufficient to address the clinical outcomes of non-metastatic prostate cancer. Thirdly, the use and duration of ADT was not uniform making it almost impossible to integrate ADT utilisation into our patient outcomes.

Conclusions

Radiation dose escalation using HDR-BT combined with EBRT is a safe and effective treatment for men with IR and HR prostate cancers. Excellent long-term bPFS, LRFS, MFS and OS were observed in patients with predominantly HR prostate cancer. The cumulative risk of late GU and GI toxicity was low and can be further improved with preventative strategies such as a pre-emptive TURP and/or HS insertion.

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Table 1. Patient characteristics

Variable	N=95 (%)
T stage	
1	18 (18.9)
2	47 (49.4)
3	30 (31.5)
ISUP grade	
ISUP grade 1	5 (5.3)
ISUP grade 2	22 (23.1)
ISUP grade 3	30 (31.5)
ISUP grade 4	15 (15.7)
ISUP grade 5	23 (24.2)
% Core Positive	
<50%	72 (75.7)
≥50%	23 (24.3)
NCCN Risk Groups	
Intermediate Risk	42 (44.2)
High Risk	53 (55.8)

ADT	
Yes	84 (88.4)
No	11 (11.6)
Prior TURP	
Yes	14 (14.8)
No	81 (85.2)
Hydrogel Spacer	
Yes	30 (31.6)
No	65 (68.4)
HDR Dose	
18Gy in 3 Fractions	24 (25.2)
16Gy in 2 Fractions	71 (74.8)

ADT: Androgen Deprivation Therapy

TURP: Transurethral Resection of the Prostate

NCCN: National Comprehensive Cancer Network

ISUP: International Society of Urological Pathology

Table 2. Univariate Analysis of Risk Factors and its impact on bPFS, MFS and OS

		Biochemical Progression Free Survival (bPFS)			Metastasis Free Survival (MFS)			Overall Survival (OS)		
Factors		**5 yr KM**	**HR (CI)**	**P Value**	**5 yr KM**	**HR (CI)**	**P Value**	**5 yr KM**	**HR (CI)**	**P Value**
Age (years)	<70	90%	0.8	0.81	92%	0.9	0.9	85%	1.0	0.99
	≥70	93%	(0.2-4.2)		92%	(0.2-4.8)		94%	(0.3-3.4)	
Tumor (T)	T1-2	92%	1.4	0.75	92%	1.4	0.70	86%	0.3	0.20
Stage	T3	91%	(0.2-8.4)		96%	(0.2-8.2)		94%	(0.1-1.1)	
ISUP (Grade)	1+2+3	91%	0.8	0.78	92%	0.96	0.96	91%	1.4	0.58
	4+5	93%	(0.2-4.1)		92%	(0.2-5.2)		84%	(0.4-4.6)	
NCCN Risk	Intermediate	92%	1.2	0.89	93%	1.1	0.92	91%	1.7	0.40
	High	88%	(0.1-11.1)		88%	(0.1-10.3)		75%	(0.4-8.2)	
Percentage	<50%	89%	0.4	0.37	91%	0.46	0.48	90%	1.3	0.70
Core +	≥50%	97%	(0.07-2.0)		97%	(0.08-2.6)		83%	(0.4-4.5)	
HDR Dose	18Gy/3F	93%	1.4	0.65	95%	1.8	0.48	87%	0.6	0.44
	16Gy/2F	89%	(0.3-7.0)		89%	(0.3-9.4)		91%	(0.2-2.0)	
ADT	No	100%	0	0.34	100%	0	0.39	80%	0.6	0.53
	Yes	90%			91%			90%	(0.1-3.8)	

HR- Hazard Ratio, KM- Kaplan Meier; ISUP- International Society of Urological Pathology, NCCN- National Comprehensive Cancer Network; HDR- High Dose Rate; ADT- Androgen Deprivation Therapy; Gy- Gray; F- Fraction

Table 3. Incidence of Acute and Late GU and GI Toxicity

	Toxicity Grade	All	No HS	HS	P value	No TURP	TURP	P value
Acute GU toxicity								
	≥Grade 1	91.6%	92.3%	83.3%	0.22	91.6%	84.6%	0.62
	Grade 2	1.1%	1.5%	0%	0.48	1.2%	0%	0.67
Acute GI toxicity								
	≥Grade 1	25.3%	30.8%	13.3%	0.05			
	Grade 2	1.1%	1.5%	0%	0.48			
Late GU toxicity								
	≥Grade 1	44%	43.1%	46.7%	0.74	41.5%	61.5%	0.18
	≥Grade 2	6.3%	7.7%	3.3%	0.4	6.1%	7.7%	0.82
	Grade 3	5.3%	6.2%	3.3%	0.57	4.9%	7.7%	0.67
Late GI toxicity								
	Grade 1	5.3%	7.7%	0%	0.11			

HS- Hydrogel Spacer; GU- Genitourinary; GI- Gastrointestinal