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Original Article

Results of 15 Gy HDR-BT boost plus EBRT in intermediate-risk prostate cancer: Analysis of over 500 patients

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ABSTRACT

Purpose/objective: To report biochemical control associated with single fraction 15 Gy high-dose-rate brachytherapy (HDR-BT) boost followed by external beam radiation (EBRT) in patients with intermediate-risk prostate cancer.

Materials and methods: A retrospective chart review of all patients with intermediate-risk disease treated with a real-time ultrasound-based 15 Gy HDR-BT boost followed by EBRT between 2009 and 2016 at a single quaternary cancer center was performed. Freedom from biochemical failure (FFBF), cumulative incidence of androgen deprivation therapy use for biochemical or clinical failure post-treatment (CI of ADT) and metastasis-free survival (MFS) outcomes were measured.

Results: 518 patients met the inclusion criteria for this study. Median age at HDR-BT was 67 years (IQR 61–72). 506 (98%) had complete pathologic information available. Of these, 146 (28%) had favorable (FIR) and 360 (69%) had unfavorable (UIR) intermediate-risk disease. 83 (16%) received short course hormones with EBRT + HDR.

Median overall follow-up was 5.2 years. FFBF was 91 (88–94)% at 5 years. Five-year FFBF was 94 (89–99)% and 89 (85–94)% in FIR and UIR patients, respectively ($p = 0.045$). CI of ADT was 4 (2–6)% at 5 years. Five-year CI of ADT was 1 (0–3)% and 5 (2–8)% in FIR and UIR patients, respectively ($p = 0.085$). MFS was 97 (95–98)% at 5 years. Five-year MFS was 100 (N/A-100)% and 95 (92–98)% in FIR and UIR patients, respectively ($p = 0.020$).

Conclusion: In this large cohort of intermediate-risk prostate cancer patients, 15 Gy HDR-BT boost plus EBRT results in durable biochemical control and low rates of ADT use for biochemical failure.

Prostate cancer is the most common non-skin malignancy diagnosed in men. Approximately 40% of patients with newly diagnosed prostate cancer are categorized in the intermediate-risk group [1]. Patients in this group have a broad spectrum of cancer aggressiveness and further subcategorization has been previously proposed [2].

Treatment options for men with intermediate risk prostate cancer include radical prostatectomy and radiotherapy. Brachytherapy (BT) given as a boost to external beam radiotherapy (EBRT) enables unparalleled dose escalation and results in higher PSA control rates than EBRT alone [3–5]. The American Society of Clinical Oncology/Cancer Care Ontario Guidelines recommends that all eligible men with intermediate or high-risk prostate cancer be offered brachytherapy boost [6]. High-dose-rate brachytherapy (HDR-BT) may be particularly effective in cancers with low alpha/beta ratios which leads to high biological tumoricidal dose with a single or few BT fractions.

A variety of dose/fractionation regimens are used for BT boost, with increasing use of single fraction HDR regimens. Data on the efficacy of single fraction boost regimens is relatively limited, with little data outside the context of a clinical trial. The purpose of this manuscript is to report the medium-term clinical outcomes of patients treated with single fraction 15 Gy HDR-BT boost followed by EBRT in patients with intermediate-risk prostate cancer.

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Materials and methods

Study design and data collection

After approval from the institutional research ethics board, data for 545 consecutive patients with intermediate-risk prostate cancer and treated with HDR-BT boost followed by EBRT between June 2009 and December 2016 at a single quaternary cancer center was retrospectively collected. Individual patient electronic medical records were reviewed. For toxicity analyses, clinical notes were reviewed and the common terminology criteria for adverse events (CTCAE) version 4.0 used to assign a toxicity grade [7].

All patients had screen detected prostate cancer and were diagnosed based on a trans-rectal ultrasound guided biopsy. A small number of biopsies invoked a transperineal approach. The majority were transrectal biopsies. All pathology underwent routine central review by a uro-pathologist. Further workup was largely based on patient risk grouping. For patients with favorable intermediate-risk (FIR) disease, typically history and physical examination, baseline PSA and digital rectal examination were deemed adequate. Patients with unfavorable intermediate-risk (UIR) disease underwent staging investigations including a bone scan and CT imaging of the chest, abdomen and pelvis. Magnetic resonance imaging was used in a minority of patients at the discretion of the treating physician.

At initial consultation, patients typically received counseling from both a urologist and a radiation oncologist with a general review of all potential treatment options. Those interested in any form of brachytherapy received a separate consultation where eligibility and contraindications were reviewed after a detailed discussion [8]. In a minority, a trans-rectal ultrasound-based volume study was used to aid with determining eligibility. Eligible patients with UIR prostate cancer were offered HDR-BT boost followed by EBRT and eligible patients with FIR prostate cancer were offered either HDR-BT boost followed by EBRT or low-dose-rate brachytherapy monotherapy.

Post treatment, PSA was measured 6-monthly for the first 2 years and then 6-monthly to yearly thereafter. All patients received HDR-BT at the study institution and were either discharged back to a regional cancer center or were typically followed for 4–5 years then discharged back to their family physician when risk of subsequent recurrence was deemed low. Prior to 2015, typically the PSA nadir and trend were used to aid with the decision to discharge patients from follow-up. In patients discharged after 2015, a PSA measurement of <0.4 after 4 years was often used to assist in determining recurrence risk [9].

Treatment characteristics

All patients within the cohort received 15 Gy in 1 fraction, HDR-BT boost to the prostate gland. This technique has previously been described [10,11]. Patients underwent general anesthetic and, under real-time trans-rectal ultrasound, 12 to 18 catheters were placed within the gland and/or proximal seminal vesicles (Supplementary Fig. 1). Sequential axial image sets were taken and used for contouring prostate (including the proximal seminal vesicles), urethra and rectal volumes and catheter reconstruction. Plans were generated using Oncentra Prostate (Elekta AB, Stockholm, Sweden) and delivered prior to anesthetic reversal. Dosimetric constraints followed a standardized in-house protocol (Supplementary Table 1) [10]. EBRT treatments were mainly hypofractionated intensity modulated radiotherapy-based plans. Dose and fractionation were at the discretion of the primary radiation oncologist, usually 37.5 Gy in 15 fractions, but ranged from 25 Gy in 5 fractions to 46 Gy in 23 fractions. For the purposes of this study, only patients that received 37.5 Gy in 15 fractions were included (518/545; 95%). Most commonly, the clinical target volume consisted of the prostate and proximal seminal vesicles. Patients did have the option to receive EBRT at centers closer to their homes. In these cases, other planning techniques were sometimes utilized.

Salvage treatment(s)

After biochemical failure was declared in a patient, PSA monitoring every 6 months was undertaken and one of two approaches were employed as further management. When the PSA reached a level between 4 and 5, it was common practice to organize bone scan, CT imaging of the chest, abdomen and pelvis and a dedicated MRI of the prostate. If disease localized to the prostate was suspected with no signs of distant metastatic disease, a biopsy was arranged. If local recurrence was confirmed, the patients were offered enrollment in an in-house salvage HDR-BT study. In cases where the patient refused, imaging tests were negative or biopsy did not confirm localized disease, the PSA was monitored until it reached any value greater than 10.0. At this point restaging investigations including a CT chest, abdomen and pelvis in addition to a bone scan were organized and either intermittent or continuous androgen deprivation therapy initiated according to the protocols described by Crook et al and Hussain et al. [12,13].

Statistical methods

Descriptive statistics were used to characterize the cohort. For continuous variables, the Shapiro-Wilk's test and density plots were used to determine normality. Normally distributed variables were described using mean (standard deviation) and non-normally distributed variables were described using median (interquartile range (IQR)). Categorical variables were presented as number (proportion).

The FIR subgroup was defined as per the National Comprehensive Cancer Network risk groupings as having one intermediate-risk factors and being grade group 1 or 2 disease with <50% of biopsy cores positive. Patients with UIR disease had either 2–3 intermediate-risk factors and/or had grade group 3 disease and/or had $\geq$50% of biopsy cores positive [14]. For comparisons between FIR and UIR subgroups Fisher's Exact test, the Fisher-Freeman-Halton test or the Mann-Whitney-Wilcoxon test were used as appropriate.

Overall follow-up was calculated as the time from HDR to any last contact with the healthcare system, PSA follow-up time was calculated as the time from HDR to any last contact where a PSA was available. For Kaplan-Meier analyses, time intervals for freedom from biochemical failure (FFBF) were calculated as time from HDR to biochemical recurrence defined as nadir + 2.0 ng/ml (Phoenix definition) or any last PSA measurement, time intervals for cumulative incidence of ADT use (CI of ADT) were calculated as time from HDR to initiation of hormonal therapy or any last follow-up and time intervals for metastasis-free survival (MFS) were calculated as time from HDR to diagnoses of metastases, death or any last follow-up [15]. Overall survival (OS) and cause specific survival (CSS) time was calculated as time from HDR to death and death from prostate cancer respectively. For survival and incidence estimates the 95% confidence interval of the estimate was also calculated. For comparisons between cohorts the Log-Rank test was used and p-values <0.05 were considered statistically significant. All statistical analyses were performed using the R programming language version 3.4.3 (www.r-project.org).

Results

518 patients met the inclusion criteria for this study. Median age at treatment was 67 (IQR: 61–72) years. Median baseline PSA was 7.3 (IQR: 5.3–9.8)ng/mL. 291 (56%) patients had cT1 and 227

(44%) had cT2 disease. 349 (67%) and 151 (29%) had Gleason grade group 2 and 3 disease respectively. In total, 146 (28%) had FIR and 360 (69%) had UIR disease. In 12 (2%) patients, there was insufficient information available to assign a risk subgrouping. Comparisons of clinical characteristics between the FIR and UIR cohorts are presented in Table 1.

A total of 83 (16%) patients received ADT for a median of 6 (IQR: 3–6) months. All patients received 15 Gy in 1 fraction HDR-BT boost and 37.5 Gy in 15 fractions EBRT. Median HDR-BT prostate volume receiving 100% of the prescribed dose (V100) was 97 (IQR: 96–97)%. Median minimum dose to the hottest 90% of the prostate volume (D90) was 16.4 (16.1–16.6)Gy. Table 2 describes the treatment received by the entire cohort in addition to the FIR and UIR subgroups.

Median overall follow-up for the cohort was 5.2 (IQR: 3.4–6.8) years. Over this period, 397 (77%) patients had both acute and late toxicity records available. Within this group, 20 (5%) patients had a maximum reported CTCAE genitourinary toxicity of grade 3. There was no grade 4 or 5 toxicity encountered. Of those with available information, 5/445 (1%) and 16/398 (4%) patients encountered a CTCAE grade 3 acute and late genitourinary toxicity, respectively. There was no grade 3 gastrointestinal toxicity encountered. Toxicity data are available in Table 3.

Median PSA nadir was 0.14 (IQR: 0.04–0.31). Median time to nadir was 3.2 (IQR: 1.8–5.0) years. At 1.5 years median PSA was 0.65 (IQR: 0.27–1.21) with 166/408 (41%) having PSA < 0.5. At 4 years median PSA was 0.20 (IQR: 0.08–0.57) with 191/283 (67%) having PSA < 0.4. PSA trend data over the first 5 years is shown in Supplementary Fig. 2.

After a median PSA follow-up time of 4.7 (IQR: 3.1–6.2) years, 47 (9%) patients experienced biochemical failure. Overall the estimated FFBF was 91 (88–94)% at 5 years (Fig. 1A). Estimated FFBF at 5 years was 94 (89–99)% and 89 (85–94)% in patients with FIR and UIR disease respectively (Fig. 1B; Log-Rank $p = 0.045$).

Of the 47 patients experiencing biochemical failure 9 (19%) underwent local salvage therapy on an institutional study protocol

Table 1
Baseline patient and disease characteristics for entire cohort, and patients with favorable and unfavorable intermediate-risk disease. Number are expressed as median (interquartile-range) or number (%) as appropriate.

	Cohort *N* = 518	Favorable *N* = 146*	Unfavorable *N* = 360*	*p*-Value
Age [years]	67 (61–72)	65 (60–71)	67 (62–72)	0.006
Baseline PSA [ng/mL]	7.3 (5.3–9.8)	6.0 (4.4–7.9)	8.0 (5.9–11.0)	<0.001
T-Stage				<0.001
T1c	291 (56%)	94 (64%)	191 (53%)	
T2a	156 (30%)	51 (35%)	99 (28%)	
T2b	64 (12%)	1 (1%)	63 (18%)	
T2c	7 (1%)	0 (0%)	7 (2%)	
Grade Group				<0.001
GG 1	9 (2%)	3 (2%)	6 (2%)	
GG 2	349 (67%)	143 (98%)	203 (56%)	
GG 3	151 (29%)	0 (0%)	151 (42%)	
Unknown	9 (2%)	0 (0%)	0 (0%)	
Positive Cores	5 (3–7)	3 (2–5)	6 (4–8)	<0.001
Cores Biopsied	12 (10–12)	12 (10–12)	12 (10–12)	0.522
% Biopsy Positive	13 (5–23)	7 (4–11)	16 (10–25)	<0.001
% Gleason Pat 4	20 (10–55)	10 (5–25)	30 (10–60)	<0.001

* 12 patients had insufficient information to stratify into the favorable or unfavorable intermediate-risk subgroups.

Table 2
Treatment characteristics for all tumors treated, and for tumors in patients with favorable and unfavorable intermediate-risk disease. Numbers are expressed as median (interquartile-range) or number (%) as appropriate.

	Cohort *N* = 518	Favorable *N* = 146*	Unfavorable *N* = 360*	*p*-Value
ADT Used				<0.001
Yes	83 (16%)	5 (3%)	76 (21%)	
No	414 (80%)	133 (91%)	273 (76%)	
Unknown	21 (4%)	8 (5%)	11 (3%)	
ADT Duration [months]	6 (3–6)	3 (3–3)	6 (3–6)	0.020
EBRT Dose [Gy] and Fractionation [#]				1.000
37.5 in 15	518 (100%)	146 (100%)	360 (100%)	
HDR Dose [Gy] and Fractionation [#]				1.000
15 in 1	518 (100%)	146 (100%)	360 (100%)	
Prostate D90 [Gy]	16.4 (16.1–16.6)	16.1 (16.1–16.6)	16.4 (16.1–16.5)	0.773
Prostate V100 [%]	97 (96–97)	97 (96–97)	97 (96–97)	0.526
Prostate V150 [%]	35 (32–38)	35 (32–38)	35 (32–38)	0.535
Prostate V200 [%]	12 (10–13)	11 (10–13)	12 (10–14)	0.099
Urethra D10 [%]	116 (115–117)	116 (115–117)	116 (115–117)	0.459
Urethra Dmax [%]	123 (120–125)	123 (120–125)	123 (120–125)	0.095
Rectum V80 [cc]	0.05 (0.00–0.21)	0.03 (0.00–0.20)	0.06 (0.00–0.24)	0.137
Rectum D10 [%]	64 (59–68)	62 (57–67)	64 (59–68)	0.160
Rectum Dmax [%]	88 (80–93)	85 (78–93)	88 (83–93)	0.186

* 12 patients had insufficient information to stratify into the favorable or unfavorable intermediate-risk subgroups.

Table 3
Any maximum reported acute and late CTCAE grade 3 genitourinary or gastrointestinal toxicity over the follow-up interval. Numbers are expressed as number (%) as appropriate.

	Acute *N* = 445	Late *N* = 398
Genitourinary Toxicity	5 (1%)	16 (4%)
Hematuria	2 (0.4%)	0 (0%)
Retention	3 (0.7%)	3 (0.8%)
Cystitis	0 (0%)	13 (3.3%)
Gastrointestinal Toxicity	0 (0%)	0 (0%)

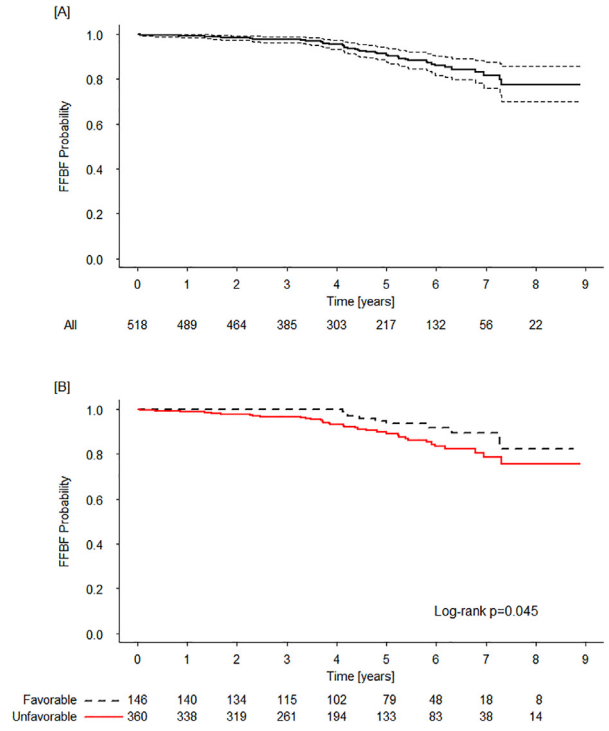

Fig. 1. Kaplan-Meier estimated freedom from biochemical failure by Phoenix definition (nadir + 2.0) in [A] all treated patients (solid line) with 95% confidence interval (dashed line) and [B] favorable (black dashed line) vs unfavorable (solid red line) intermediate-risk subgroups.

and of these, 4 (44%) eventually required ADT for biochemical failure.

After a median overall follow-up of 5.2 (IQR: 3.4–6.8) years, 20 (4%) patients received ADT for biochemical failure. CI of ADT use at 5 years was 4 (2–6)% (Fig. 2A). Estimated CI of ADT use at 5 years was 1 (0–3)% and 5 (2–8)% in patients with FIR and UIR disease respectively (Fig. 2B; Log-Rank $p = 0.085$).

Of the 20 patients receiving ADT for biochemical failure, 3 (15%) developed castrate resistant disease. Castrate resistance was experienced after 1.3, 2.7, and 4.2 years of ADT.

11 (2%) patients developed metastatic disease. Of these 3 (1%) had skeletal, 4 (1%) had visceral and 4 (1%) had both visceral and skeletal mets identified as the first site of metastatic disease. Metastatic disease was encountered after a median of 4.4 (3.5–5.9) years in these patients. Kaplan-Meier estimated 5 year MFS was 97 (95–98)% (Fig. 3A). Estimated 5 year MFS was 100 (N/A-100)% and 95 (92–98)% in patients with FIR and UIR disease respectively (Fig. 3B; Log-Rank $p = 0.020$).

In total, 12 (2%) patient deaths were recorded during the follow-up period. Kaplan-Meier estimated 5 year OS was 98 (97–99)% (Supplementary Fig. 3A). Estimated 5 year OS was 99 (99–100)% and 96 (94–99)% in FIR and UIR disease respectively (Supplementary Fig. 3B; Log-Rank $p = 0.275$).

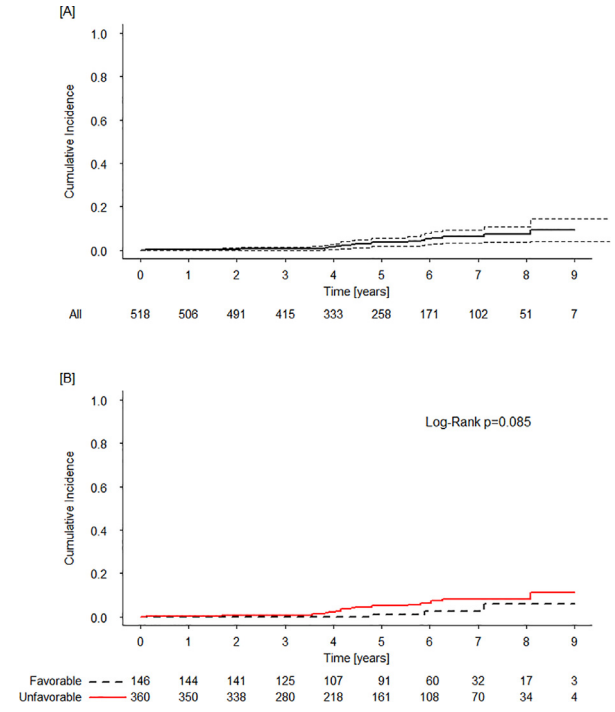

Fig. 2. Cumulative incidence of ADT use for biochemical failure in [A] all treated patients (solid line) with 95% confidence interval (dashed line) and [B] favorable (black dashed line) vs unfavorable (solid red line) intermediate-risk subgroups.

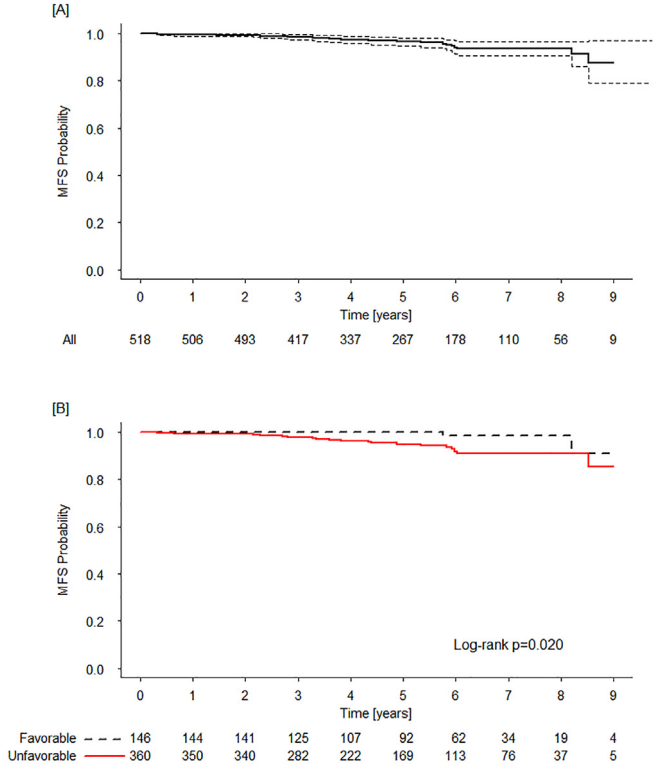

Fig. 3. Kaplan-Meier estimated metastasis-free survival in [A] all treated patients (solid line) with 95% confidence interval (dashed line) and [B] favorable (black dashed line) vs unfavorable (solid red line) intermediate-risk subgroups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In one (0%) patient, the cause of death was identified as prostate cancer. In this patient, biochemical failure was declared at

4 months, metastatic disease diagnosed at 6 months and death occurred 1.7 years post treatment. For the cohort, Kaplan-Meier estimated 5 year CSS was 100 (99–100)% (Supplementary Fig. 4A). Estimated 5 year CSS was 100 (N/A-100)% and 100 (99–100)% in FIR and UIR disease respectively (Supplementary Fig. 4B; Log-Rank $p = 0.521$).

Discussion

This is a large, single institutional retrospective cohort study of patients with intermediate-risk prostate cancer treated with external beam radiotherapy and HDR-BT boost.

The treatment regimen used in this cohort has previously been reported in a prospective clinical trial which demonstrated low morbidity and high biochemical control (97% 5-year FFBF) when compared to more fractionated HDR-BT boost regimens [10,11,16]. The present study reflects real world outcomes of single fraction HDR-BT boost followed by EBRT in a large cohort of patients ($n = 518$). It reports on trans-rectal ultrasound-based planning as opposed to CT-based planning as used in the clinical trial. These favorable outcomes further support the use of single fraction HDR-BT boost regimens especially given their convenience and low resource utilization.

When considering the rationale for this treatment, it is important to note that previous randomized data have indicated that brachytherapy boost improves biochemical control when compared to EBRT alone [3–5]. Hoskin et al. have specifically looked at the HDR-BT boost strategy in patients with intermediate and high-risk disease. In the Hoskin study there was noticeable improvement in bRFS for the BT boost arm with a median time to relapse of 116 months versus 74 months in the EBRT arm. At 7-years out from treatment bRFS was 66% versus 48% for the EBRT group indicating a long-term persistent difference.

In the present study, only patients with intermediate-risk prostate cancer were reviewed. When the results observed in this cohort are compared with other reported intermediate-risk cohorts treated with HDR-BT, biochemical control generally appears similar (Table 4) [4,17–32]. This is despite variation in the definition of biochemical failure over the time periods examined. Furthermore, the biochemical control in the present study seem superior to current non-brachytherapy standard options including hypofractionated single modality EBRT [33,34]. The improvement in prostate cancer control with the addition of brachytherapy is shown in several studies and published outcomes for brachytherapy with EBRT are consistently superior to those for EBRT alone [3–5,35,36]. In perhaps the most striking of these studies, prostate cancer mortality benefit was established in patients with Gleason 9–10 disease by Kishan et al (cumulative incidence of prostate cancer deaths 3% vs 11%) [35].

The biochemical outcomes encountered in the present study (91% FFBF at 5 years) are further supported by the low median PSA nadir (0.12). Tsumura et al. have previously shown that in patients with high-risk prostate cancer and PSA nadir values ≤ 0.02 had a 94% chance of biochemical control 7 years after receiving HDR-BT [37]. Furthermore, measured PSA values of <0.5 18 months after HDR-BT boost have been strongly correlated with improved PSA disease free survival [38]. In the present study, 41% of patients had PSA < 0.5 at 18 months. However, one should exercise caution when interpreting this as benign bounce events typically occur within the first 2 years post treatment. In the present study, PSA decline continued after 1.5 years with 67% having PSA < 0.4 at 4 years, a benchmark that has been correlated with longer-term biochemical control in other radical radiotherapy treatment settings for prostate cancer [39-41]. Given this, the current study's excellent outcomes are likely sustainable over a longer period of time.

Many brachytherapy studies do not report the use of salvage ADT after biochemical failure. This is a potentially useful clinical endpoint of relevance to patients as long-term intermittent and continuous ADT are associated with considerable morbidity [13,42]. Only 4% of patients required ADT for biochemical failure after use of HDR-BT. This low rate might be for two possible reasons. First, the study center has a considerable experience with salvage brachytherapy and most eligible patients for salvage therapy would be worked up and offered salvage (usually without ADT) if they had local failure [43]. Secondly, patients not eligible or interested in local salvage were typically managed with intermittent androgen blockade after the PSA rose above 10 ng/ml [42].

When considering the FIR and UIR cohorts, the differences CI of ADT use (1% vs 5%; p = 0.085) found between cohorts were not statistically significant. The small differences in FFBF (94% vs 89%; $p = 0.045$) and MFS (100% vs 95% at 5 years; $p = 0.020$) observed were statistically significant. This supports the concept that a small difference in oncological outcome between patients with FIR and UIR prostate cancer persists even when dose escalation with HDR-BT boost combined with EBRT is used. A similar difference was found by Berlin et al. in patients receiving radical prostatec-

Table 4
Summary of selected studies reporting outcomes from HDR-BT in patients with intermediate-risk prostate cancer.

Study	Treatment Years	No. Patients	Risk Group	HDR	EBRT	Time	Outcome Reported*	Outcome
Neviani et al.[17]	2000–2004	120	Int	6–6.5 Gy × 3	1.8 Gy × 25	5-year	bRFS	86.9%
Hoskin et al. [4,25]	1997–2005	110	Low-High	8.5 Gy × 2	2.75 Gy × 13	5-year	bRFS	75%
Chen et al. [26]	2000–2004	31	Int	5.5 Gy × 3	1.8 Gy × 28	4-year	bFFS	91%
Phan et al. [18]	1996–2006	109	Int	5–6 Gy × 3–4	1.8–2.0 Gy × 13–28	5-year	bC	90%
Kotecha et al.[19]	1998–2010	141	Int	5.5–7 Gy × 3	1.8 Gy × 25–28	7-year	bRFS	90%
Aluwini et al. [20]	2000–2007	264	Low-Int	6 Gy × 3	1.8 Gy × 25	7-year	bFFS	97%
Yaxley et al. [21]	2000–2009	169	Int	6.5 Gy × 3	2 Gy × 23	5-year	bNED	93%
Martinez et al. [22]	1992–2007	472	Int-High	8.75–11.5 Gy × 2	2 Gy × 23	10-year	CI-BF	19%
Bachand et al. [27]	1999–2006	126	Low-Int	6–10 Gy × 2–3	2 Gy × 20–22	5-year	bRFS	96%
Joseph et al. [28]	2008–2010	34	Int	12.5 Gy × 1	2.5 Gy × 15	5-year	bDFS	82%
Cury et al. [29]	2001–2008	121	Int	10 Gy × 1	2.5 Gy × 20	5-year	bRFS	91%
Boladeras et al. [30]	2002–2012	271	30 Int-241 High	9 Gy × 1	2 Gy × 30	5-year	bRFS	91%
Astrom et al. [31]	1995–2008	201	Int	10 Gy × 2	2 Gy × 25	10-year	CI-BF	21%
Galalae et al. [32]	1986–1999	324	Int-High	5.5–15 Gy × 2–3	1.8–2 Gy × 25–26	5-year	bC	79%
Lilleby et al. [23]	2004–2011	19	Int	10 Gy × 1–2	2 Gy × 25–30	5-year	bFFS	100%
Khor et al. [24]	2001–2006	203	Int	6.5 Gy × 3	2 Gy × 23	5-year	bFFS	84%
Martell/Mendez et al.	2009–2016	518	Int	15 Gy × 1	2.5 Gy × 15	5-year	FFBF	91%

* bRFS – biochemical relapse free survival; bFFS – biochemical failure free survival; bDFS – biochemical disease free survival; CI-BF – cumulative incidence of biochemical failure; bC – biochemical control; bNED – biochemical no evidence of disease; FFBF – freedom from biochemical failure.

tomy, dose escalated EBRT or low-dose-rate brachytherapy monotherapy [44]. In their study, cumulative incidence of metastatic disease ranged from 0-0.8% and 3.1–4.2% at 5 years for the 1063 and 1487 patients with FIR and UIR prostate cancer respectively. In the Berlin et al. study development of metastatic disease between patients with FIR and UIR prostate cancer differed significantly in the radical prostatectomy (n = 1127) and EBRT (n = 1143) arms but not in the brachytherapy arm (n = 258).

The toxicity encountered in the current study is similar to that reported by Morton et al. in patients receiving CT based HDR-BT [10]. In the former study only 2% of cases had grade 3 acute retention were noted and no grade 3 late toxicity was encountered. In a follow-up study reporting on the late toxicity rates for the same 125 men, 2% rates of retention and hematuria were encountered. Additional 1% of patients had CTCAE v3 retention and bladder pain [45]. Accounting for the difference in CTCAE v3 and v4, the present study (with almost 400 patients having sufficient late toxicity data) supports the results of both of these studies and establishes ultrasound planned 15 Gy HDR-BT combined with EBRT as a well-tolerated treatment with very low rate of late toxicity.

The current study has several limitations inherent to its retrospective nature. Of particular importance, this analysis would be susceptible to underreporting of toxicity data. Additionally, it may be prone to a follow-up bias as patients with good biochemical control were typically discharged at 4–5 years post treatment. Furthermore, the overall median follow-up in this cohort was short (5.2 years). With these two confounders, this study lacks the ability to reliably predict for long-term FFBF or MFS in patients treated with HDR-BT and EBRT. Also, these results are single institutional and from a high-volume, North American brachytherapy center. They may not be transferable to centers with small caseloads or differing patient populations.

In conclusion, this large cohort of patients with intermediate-risk prostate cancer showed that treatment with 15 Gy in 1 fraction HDR-BT followed by 37.5 Gy in 15 fractions EBRT leads to good biochemical control and low rates of ADT use for failure. The outcomes encountered here are superior to those found when EBRT alone is used. The rates of medically significant or severe toxicity were low. Finally, in the present study HDR-BT with EBRT was utilized for treatment of FIR and UIR patients. While, standard inclusion of BT with EBRT should be considered for UIR and high-risk disease, low-dose-rate brachytherapy, or multifraction HDR-BT regimens should be considered for patients with FIR disease given the simplicity of treatment and proven efficacy.

Conflict of interest

There is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.08.017.

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