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Prostate Virtual High-dose-rate Brachytherapy Boost: 5-Year Results from the PROMETHEUS Prospective Multicentre Trial

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Abstract

Background and objective: Despite the high efficacy of high-dose-rate brachytherapy boost (HDRB) in the management of prostate cancer (PC), use of this approach is declining. Similar dosimetry can be achieved using stereotactic body radiotherapy or "virtual HDRB" (vHDRB). The aim of the multicentre, single-arm, phase 2 PROMETHEUS trial (ACTRN12615000223538) was to evaluate the safety and efficacy of vHDRB in patients with PC.

Methods: Patients with intermediate-risk PC or selected patients with high-risk PC were eligible for inclusion. vHDRB was given as 19–20 Gy in two fractions, delivered 1 wk apart, followed by conventionally fractionated external beam radiotherapy (EBRT) at 46 Gy in 23 fractions or 36 Gy in 12 fractions. The primary endpoint was the biochemical/clinical relapse–free rate (bcRFR). Toxicity was graded using Common Terminology Criteria for Adverse Events version 4 and quality of life (QoL) data were collected used the Expanded Prostate Cancer Index Composite-26 questionnaire.

Key findings and limitations: From March 2014 to December 2018, 151 patients (74% intermediate risk, 26% high risk) with a median age of 69 yr were treated across five centres. Median follow-up was 60 mo. The 5-yr bcRFR was 94.1% (95% confidence interval [CI] 90–98%) and the local control rate was 98.7%. Acute grade 2 gastrointestinal (GI) and genitourinary (GU) toxicity occurred in 6.6% and 23.2% of patients, respectively, with no acute grade 3 toxicity. At 60 mo after treatment, the prevalence of late grade $\geq$2 GI toxicity was 1.7% (95% CI 0.3–6.5%) and the prevalence of late grade $\geq$2 GU toxicity was 3.3% (95% CI 1.1–8.8%). Between baseline and 60 mo, QoL improved for urinary obstructive and hormonal domains, was stable for the bowel domain, and deteriorated slightly for the sexual and urinary incontinence domains.

Conclusions: Delivery of gantry-based vHDRB followed by conventionally fractionated EBRT is feasible in a multicentre setting, with high 5-yr bcRFR and low toxicity. This approach is being compared with prostate ultrahypofractionated radiotherapy in the TROG 18.01 NINJA randomised trial (ACTRN12618001806257).

Patient summary: The PROMETHEUS trial investigated noninvasive high-dose precision radiotherapy combined with conventional radiotherapy in patients with prostate cancer.

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We found that this new technique was well tolerated and resulted in better cancer control outcomes than historically reported.
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1. Introduction

Prostate cancer (PC) is the most common invasive malignancy affecting men worldwide, with an estimated lifetime risk of one in eight [1]. In various randomised trials, brachytherapy has been used for radiation dose escalation and has consistently demonstrated superior disease control compared to standard doses of external beam radiotherapy (EBRT) [2–4]. However, despite its efficacy, the use of brachytherapy for the treatment of PC has experienced a significant decline on an international level [5,6]. Meanwhile, technological progress has resulted in the emergence of advanced radiotherapy (RT) techniques capable of delivering accurate high doses of radiation within a limited number of treatment sessions. This stereotactic body RT (SBRT) technique has been extensively studied over the past two decades as a management strategy for PC [7–9].

High-quality trials comparing SBRT monotherapy to conventional RT have recently been reported. The phase 3 HYPO-RT-PC randomised controlled trial (RCT) [8] compared 78 Gy in 39 fractions to 42.7 Gy delivered over seven sessions. The study showed that both approaches resulted in an equivalent 5-yr biochemical progression-free survival (PFS) rate of 84% (95% confidence interval [CI] 80–87%), with an adjusted hazard ratio (HR) of 1.002 (95% CI 0.758–1.325; log-rank $p = 0.99$). The more frequently used five-fraction SBRT approach is also under investigation, with initial results emerging from the PACE-B phase 3 RCT [9]. The PACE-B study involved comparison of either 78 Gy in 39 fractions or 62 Gy in 20 fractions with 36.25 Gy in five fractions. Preliminary outcomes revealed comparable 2-yr Radiation Therapy Oncology Group toxicity rates between the two groups, and efficacy data showed noninferiority of the 5-yr disease control rate (94.6% for conventional vs 95.7% for SBRT; $p = 0.007$) [10].

A virtual high-dose-rate brachytherapy boost (vHDRB) uses an SBRT boost in addition to conventional RT. The underlying principle is to mimic a brachytherapy boost noninvasively, with the aim of achieving efficacy outcomes similar to those seen in the landmark ASCENDE-RT trial [11], in which the biochemical relapse rate halved in the brachytherapy boost cohort, but ideally without the increase in the cumulative incidence of severe, grade 3 genitourinary (GU) toxicity seen in this RCT at 5 yr (18.4% vs 5.2%;$p < 0.001$). Although numerous studies have used vHDRB, these were typically single-institution studies with small numbers. Great heterogeneity for all aspects of this technique remains [12].

Here we report 5-yr outcomes from the multicentre, prospective, phase 2 PROMETHEUS trial (Prostate Multicenter External beam Radiotherapy Using Stereotactic Boost; ACTRN12615000223538).

2. Patients and methods

2.1. Study design and participants

The PROMETHEUS trial recruited patients from five Australian centres between March 2014 and December 2018. It aimed to assess the effectiveness and safety of combining conventional fractionated EBRT with vHDRB in patients with intermediate-risk or high-risk PC. The study protocol has been published and used a standard gantry-based linear accelerator solution [13].

Eligible participants had a confirmed histological diagnosis of prostate adenocarcinoma with intermediate- or high-risk stage according to National Comprehensive Cancer Network (NCCN) guidelines and an Eastern Cooperative Oncology Group performance status score of 0–1. Participants were ineligible if they had clinical T4 disease, nodal or distant metastases, severe obstructive urinary symptoms that necessitated catheterisation or transurethral resection of the prostate (TURP) before RT, a history of pelvic RT, inflammatory bowel disease, or a hip prosthesis, or of they were unable to undergo magnetic resonance imaging (MRI) or fiducial marker insertion. Prior TURP before diagnosis was allowable. Patients with high-risk stage had to undergo either prostate-specific membrane antigen (PMSA) positron emission tomography (PET) imaging or conventional staging with computed tomography (CT) of the abdomen and pelvis, and a whole-body bone scan.

The study received ethics approval from the South Western Sydney Local Health District Human Research Ethics Committee (2019/ETH04142), and written informed consent was obtained from all participants before their inclusion in the study.

2.2. Procedures

Use of a rectal displacement device was mandatory, with the option for either a SpaceOAR (Augmenix, Waltham, MA, USA) or a Rectafix (Scanflex Medical AB, Tumstocksvägen, Sweden) device. If Rectafix was used, it was only used for the vHDRB fractions. Mandatory components of the treatment included planning MRI, placement of fiducial markers, and intrafraction image guidance. Use of an indwelling catheter to aid delineation of the urethra was optional.

The clinical target volume and details on expansions to the planning target volume for both the conventional and vHDRB fractions are included in the Supplementary material. The prescribed dose for vHDRB was 19–20 Gy delivered in two fractions, spaced 1 wk apart. The dose specifications and constraints have already been reported [14]. Intrafraction image guidance was achieved via ExacTrac, Triggered Imaging, mid-treatment cone-beam CT, or in-house soft-

ware for real-time continuous kilovoltage tracking of the fiducial marker (SeedTracker) [15,16].

The second-phase EBRT component commenced 2 wk after vHDRB. Elective pelvic nodal irradiation was recommended if the estimated risk of nodal involvement was >15% according to the Memorial Sloan Kettering Cancer Center nomogram [17]. The prescribed dose was 46 Gy in 23 daily fractions or 36 Gy in 12 daily fractions, with daily image guidance.

The decision regarding the type and duration of androgen deprivation therapy (ADT) was left to investigator discretion. The quality assurance protocol for contouring and plan reviews has already been reported [14].

Data for prostate-specific antigen (PSA) and toxicity evaluations according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4 were gathered before treatment initiation, on treatment completion, at 6 wk after treatment, and then every 6 mo for up to 5 yr. Quality of life (QoL) data using the Expanded Prostate Cancer Index Composite short form (EPIC-26) [18] were collected at baseline, at the end of RT, and 12, 36, and 60 mo after RT. EPIC-26 scores were rescaled to a 0–100-point scale, with higher scores representing better QoL [19].

2.3. Outcomes

The primary objective of the study was to determine the safety and efficacy of vHDRB. The primary endpoint was the biochemical/clinical relapse-free rate (bcRFR), which is a composite of biochemical control defined according to the Phoenix criterion (PSA nadir + 2 ng/ml) sustained at subsequent assessments [20], evidence of disease progression on imaging, or initiation of subsequent therapies. A cumulative incidence rate of >15% for grade 3 gastrointestinal (GI) or GU toxicity, excluding erectile dysfunction, was set as a criterion for stopping the study. A prevalence rate of <15% for late grade $\geq$2 GI or GU toxicity over the 5 yr of follow-up was considered acceptable. When the trial was approaching 5 yr of accrual, the trial management committee met and recommended cessation of further accrual owing to low rates of grade 3 toxicity events and the prohibitive time frame for completing the 60-mo follow-up for all 151 original patients.

Secondary endpoints related to patient-reported outcomes were EPIC-26 composite scores (bowel, urinary, sexual, and hormonal), which were reported as a score out of 100 and compared between baseline and specified time points using the Mann-Whitney *U* test.

3. Results

Between March 2014 and December 2018, 163 patients were screened across five centres and consented to the trial. Twelve withdrew or were excluded from the trial for the reasons listed in Supplementary Table 1. Therefore, 151 patients proceeded with RT.

Of these 151 patients, 141 completed a minimum of 4 yr of study follow-up, with the remainder censored. The median follow-up was 60 mo, with 120 patients completing all 60 mo of follow-up. Those censored included five men who died of non-PC causes, three diagnosed with a new cancer, and three who declined follow-up or re-consent or relocated. A CONSORT diagram for the study is shown in Supplementary Figure 1. No treatment-related or PC-related deaths were reported. Baseline demographics and clinical and treatment characteristics are presented in Table 1.

3.1. Primary endpoint: bcRFR

At median follow-up of 60 mo, eight patients had experienced biochemical and/or clinical failure, giving a bcRFR of 94.1% (95% CI 90–98%; Fig. 1). Of these eight patients, one declined imaging, one had negative imaging, three had bone-only metastases, one had both bone and nodal metastases, and two had only local failure (Table 2).

The local control rate was 98.7% (95% CI 99.8–94.8%), with the two local failures occurring at the initial site of disease, the original dominant intraprostatic lesion (DIL). All location failures were identified on PSMA PET.

The PSA response after vHDRB in the non-ADT group (n = 68) was a near-ablative response, as shown in Figure 2. Thirteen patients (8.6%, 95% CI 4.9–14.6%) had a PSA rise of >1 ng/ml, of whom six (46%) had a PSA rise of >2 ng/ml, which subsequently fell, consistent with a benign reaction to the RT rather than disease progression. Of these, ten

Table 1 – Baseline demographics and clinical and treatment characteristics

Parameter	Result
Median age at enrolment, yr (range)	69 (53–85)
Clinical T stage, *n* (%)	
cT1	61 (40.4)
cT2	72 (47.7)
cT3	18 (11.9)
Gleason score and grade group, *n* (%)	
Gleason 6 (ISUP GG 1)	3 (2.0)
Gleason 7 (ISUP GG 2/3)	117 (77.5)
Gleason 8 (ISUP GG 4)	15 (9.9)
Gleason 9 (ISUP GG 5)	16 (10.6)
NCCN risk category, *n* (%)	
Intermediate	112 (74.2)
High	39 (25.8)
Androgen deprivation, *n* (%)	
None	68 (45.0)
≤6 mo	55 (36.4)
>6	28 (18.6)
Rectal separation, *n* (%)	
SpaceOAR	94 (62.3)
Rectafix	56 (37.1)
Unknown/unreported	1 (0.7)
SBRT dose level, *n* (%)	
19 Gy	42 (27.8)
20 Gy	109 (72.2)
EBRT dose schedule, *n* (%)	
36 Gy in 12 fractions	16 (10.6)
46 Gy in 23 fractions	134 (88.7)
Other	1 (0.7)
Elective pelvic EBRT, *n* (%)	
No	136 (90.1)
Yes	15 (9.9)
TURP before radiotherapy, *n* (%)	
No	137 (90.7)
Yes: 0–1 yr	6 (4.0)
Yes: >2 yr	8 (5.3)

ISUP GG = International Society of Urological Pathology grade group; NCCN = National Comprehensive Cancer Network; SBRT = stereotactic body radiotherapy; EBRT = external beam radiotherapy; TURP = transurethral resection of the prostate.

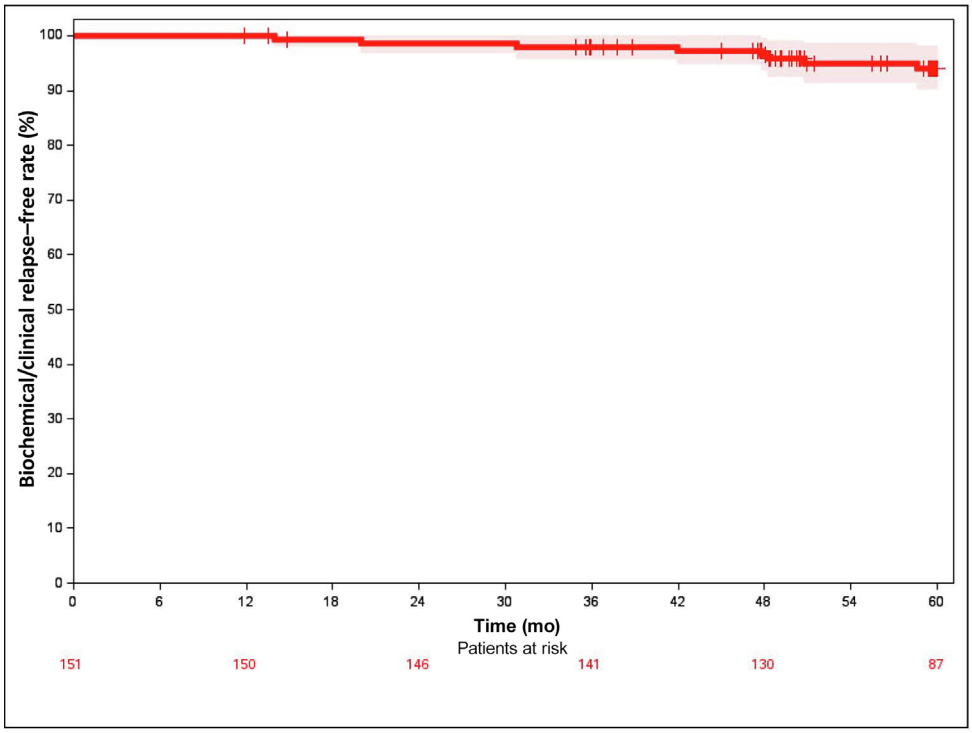


Fig. 1 – Biochemical/clinical relapse–free rate.

Table 2 – Biochemical and/or clinical failure details by patient

Patient	Relapse details	Time of BCF	Original disease features			Age (yr)	Other features
			GS	Stage	iPSA (ng/ml)		
1	Declined imaging, PSA continued to rise	42 mo	7	T1b	8.6	77	TURP, no ADT
2	Bone	20 mo	8	T2c	14.18	78	TURP, 6 mo of ADT
3	Local	31 mo[a]	8	T1c	9.2	80	6 mo of ADT
4	Negative conventional and PSMA imaging; PSA continued to rise	51 mo	7	T2b	11.4	72	6 mo of ADT
5	Bone and nodal	48 mo	7	T3b	8.75	70	TURP, 6 mo of ADT
6	Bone	48 mo[a]	7	T2a	8.3	73	6 mo of ADT
7	Bone	14 mo	7	T2b	16.5	67	No ADT
8	Local	59 mo	7	T1c	14	71	No ADT

BCF = biochemical failure; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; GS = Gleason score; iPSA = initial PSA; TURP = transurethral resection of the prostate; ADT = androgen deprivation therapy.
[a] Failure detected on imaging at a PSA rise below the Phoenix criterion.

occurred at 12-mo follow-up, two at 18-mo follow-up, and one at 24-mo follow-up. The median magnitude of the PSA bounce was 1.78 ng/ml.

3.2. Acute toxicity incidence

Acute grade 2 GU toxicity at the end of RT occurred in 35/151 patients (23.2%, 95% CI 16.9–30.9%). This decreased to eight of 151 patients (5.3%, 95% CI 2.5–10.5%) at 6 wk following treatment completion. Acute grade 2 GI toxicity occurred in ten of 151 patients (6.6%, 95% CI 3.4–12.2%) at the end of RT. This decreased to three of 151 patients (2.0%, 95% CI 0.5–6.2%) at 6 wk following treatment completion. There was no acute grade 3 GI or GU toxicity reported.

3.3. Late toxicity prevalence

The prevalence of grade ≥2 late GI toxicity did not exceed 4% at any time point (Fig. 3A). The prevalence of grade ≥2 late GU toxicity did not exceed 15% at any time point (Fig. 3B), although we noted a subacute flare between 12 and 18 mo following treatment that had largely subsided by the 24-mo assessment. At last follow-up, all grade 3 toxicities had either improved or resolved. Persistent late toxicity was rare: at 5 yr there was the rate of grade 2 GU toxicity was 3.3% (95% CI 1.1–8.8%) and the rate of grade 2 GI toxicity was 1.7% (95% CI 0.3–6.5%).

Overall, seven patients experienced grade 3 toxicity. The first developed radiation necrosis of the bladder trigone at 12 mo and underwent successful treatment using hyper-

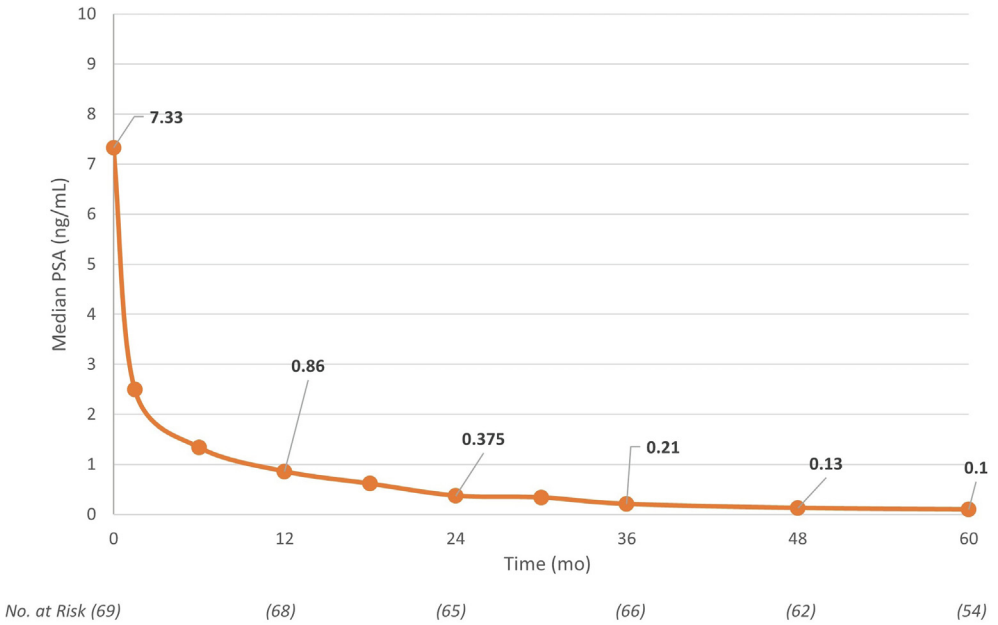


Fig. 2 – Prostate-specific antigen (PSA) response after treatment in the cohort not receiving androgen deprivation therapy.

baric oxygen therapy (HBO), with resolution by 18-mo follow-up. This patient had undergone TURP >2 yr before RT. The second patient developed severe proctitis at 12 mo, which was treated with HBO; this patient also developed severe cystitis at 24 mo and underwent further HBO. After the last HBO treatment, these toxicities had resolved by the next follow-up visit. This patient had also undergone TURP >2 yr before RT. The third patient underwent an elective Rezūm procedure after RT and developed urinary incontinence affecting activities of daily living at 48-mo follow-up. The fourth patient was experiencing worsening obstructive urinary symptoms at 36-mo follow-up and underwent urethral dilatation for stenosis, presumed to be related to urethral stricture formation. The fifth patient reported persistent severe irritative urinary symptoms, haematuria, and perianal pain at 18-mo follow-up, which resolved after HBO treatment. This patient had undergone TURP >2 yr before RT. The sixth patient developed haematuria and clot retention requiring admission to hospital at 18 mo, with discharge the next day. The last patient had developed grade 3 proctitis, noninfective cystitis, and urinary incontinence by 18-mo follow-up. These had resolved at the next follow-up after HBO therapy. These data support the position that TURP before RT is not a contraindication for vHDRB, but patients who undergo TURP may experience a small increase in the risk of an adverse event.

3.4. QoL according to EPIC-26 scores

Median EPIC-26 QoL scores were analysed for the urinary incontinence, irritative or obstructive urinary symptoms, bowel, sexual, and hormonal composite scales (Fig. 4). The median (± standard deviation) score for irritative or obstructive urinary symptoms significantly declined from baseline (93.75 ± 12.53) to the end of treatment (75 ± 17.32; $p < 0.001$), then returned to normal and showed improvement at 60 mo (100 ± 11.51; $p = 0.005$). The decline in urinary incontinence scores from 100 ± 14.72 at baseline reached statistical significance at 60 mo (88.63 ± 21.17; $p = 0.008$). Baseline bowel scores (100 ± 9.00) had significantly declined by the end of treatment (91.67 ± 16.04; $p < 0.001$) and then returned to baseline by 36 mo. The baseline score for the sexual domain (30.5 ± 31.60) had the largest standard deviation among the QoL data. Despite this, a decline was noted at 60 mo (18 ± 26.00; $p = 0.059$). The hormonal QoL score was 90 ± 15.81 at baseline and had significantly declined by the end of treatment (85 ± 17.12; $p < 0.001$). This improved at 12 mo and was maintained at 60 mo (95 ± 12.4; $p = 0.153$).

4. Discussion

Our prospective study has demonstrated impressive 5-yr outcomes for vHDRB using 19–20 Gy in two fractions across multiple centres. This treatment modality had high efficacy, with a 5-yr bcRFR of 94.1%; only two patients experienced local failure. To the best of our knowledge, this is the largest prospective multicentre cohort for vHDRB, and the encouraging efficacy warrants further investigation of this treatment approach.

The trial regimen was well tolerated, with very low GI toxicity and stable GI QoL. Interestingly, a triphasic GU toxicity profile was observed for vHDRB. Acute RT GU toxicities are well known. However, irritative GU toxicity at 12–18 mo after treatment was observed in just 12% of patients. Similar subacute GU toxicity has been observed in other studies, such as the SBRT arm of the PACE-B study [9]. This subacute toxicity largely resolved within 6 mo and did not translate into late toxicities over the subsequent 3 yr of follow-up. Partly because of the transient nature of both acute and subacute toxicities, we did not consider that

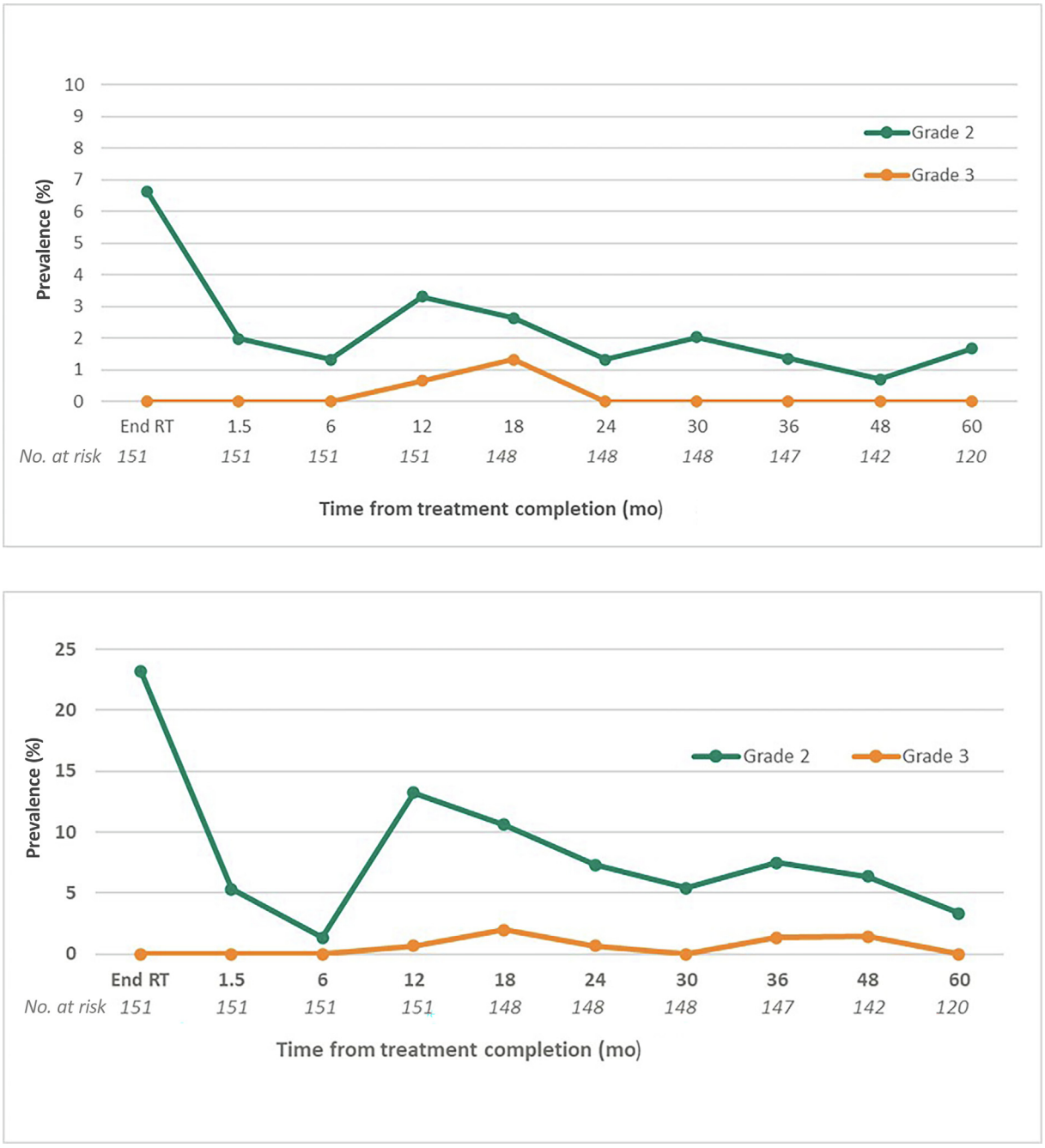


Fig. 3 – Prevalence of acute (end of RT to 1.5 mo) and late (6–60 mo) toxicity events according to Common Terminology Criteria for Adverse Events v4 for (A) gastrointestinal and (B) genitourinary toxicity. RT = radiotherapy.

cumulative toxicity rates would be informative, given that the vast majority of toxicities resolve spontaneously. Grade 3 GU toxicities were rare in comparison to the 18.4% rate noted in the ASCENDE-RT trial [11]; all had resolved by 5-yr follow-up, and HBO therapy proved to be an effective treatment for the more intractable cases.

Our protocol allowed stepwise dose escalation of the SBRT component from a starting point of 19 Gy to 20, 21, and finally 22 Gy. After completion of accrual to the 20-Gy cohort, the trial management committee noted both the near-ablative PSA responses among the initial patients accrued and the emerging efficacy evidence for 40 Gy in five fractions, which is roughly isoequivalent to our regimen of 20 Gy in two fractions. On the basis of our results, we would not recommend further whole-gland dose escalation beyond 20 Gy.

PSA bounces occurred in a significant minority of patients managed with vHDRB. These bounces happened when PSA levels were declining but were still >1.0 ng/ml. The majority (77%) of bounces occurred at 12-mo follow-up, and none were seen beyond 24 mo. The largest bounce observed in this patient group rose from 2.3 ng/ml to 12 ng/

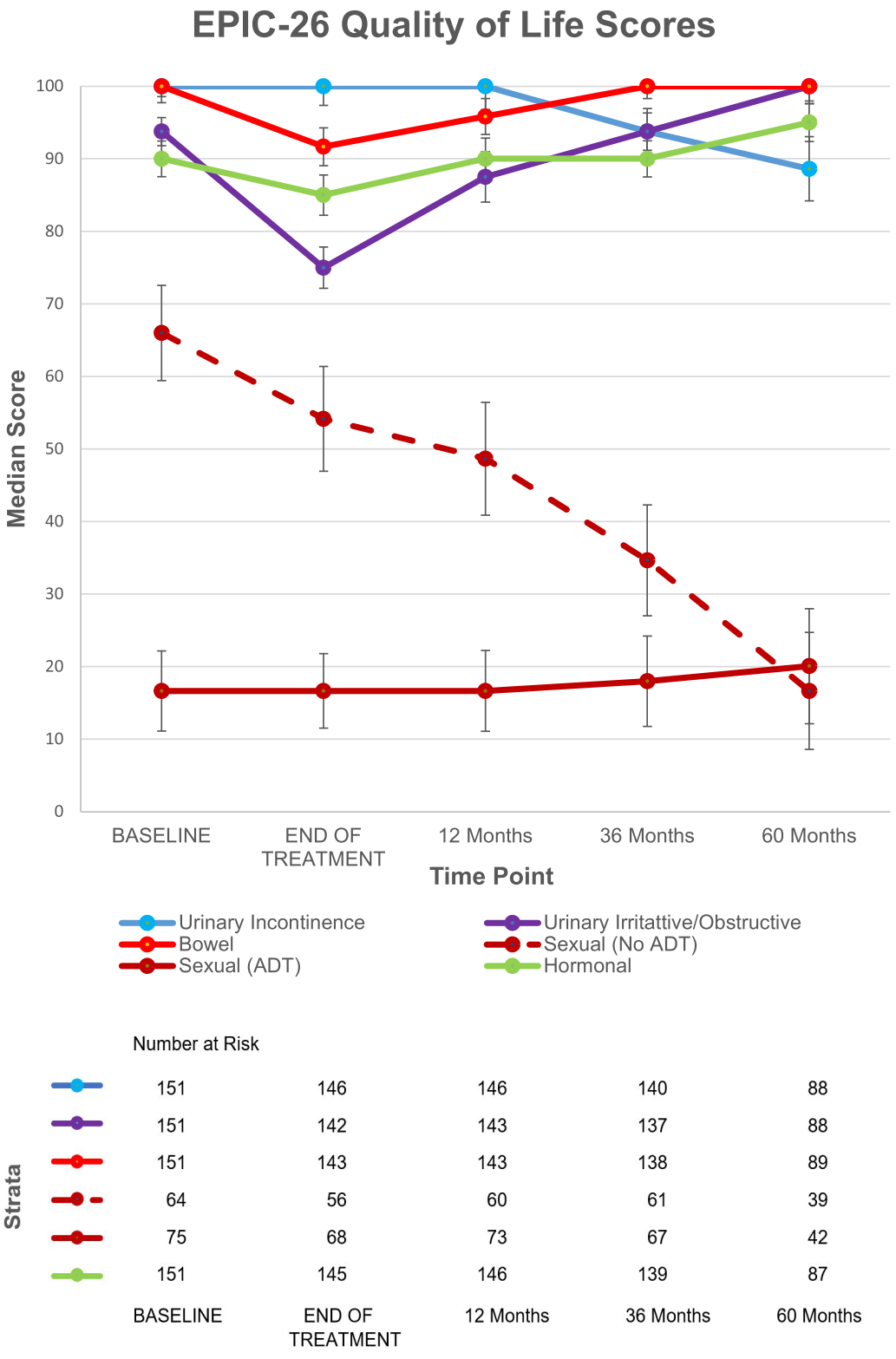


Fig. 4 – Median quality-of-life scores for the Expanded Prostate Cancer Index Composite-26 questionnaire. Error bars indicate the interquartile range. Individual domain scores and the minimal clinically important changes are presented in Supplementary Figure 3. ADT = androgen deprivation therapy.

ml; after normal PSMA PET findings were observed, the PSA level subsequently declined and was 0.19 ng/ml at last follow-up. Clinicians need to be aware of this possibility so they do not trigger salvage therapies without further evidence from imaging or biopsy of clinical disease progression.

Our trial results are comparable to those from other studies that used vHDRB. The CKNO-PRO trial used vHDRB of 18 Gy in three fractions. The grade ≥2 GU toxicity was 1.3% (CI 0.1–6.4) at median follow-up of 88 mo and the grade ≥2 GI toxicity was 11.0% (95% CI 5.1–19.4%) at 120 mo. The higher GI toxicity in this trial may be related to the lack of rectal spacing and our use of more stringent rectal dosimetry constraints. The 96-mo relapse-free survival rate for this intermediate risk population was 76.9% (95% CI 63.1–86.1%) [21]. The relatively low GU toxicity and higher failure rate may be related to the lower biological dose of radiation delivered (Supplementary Table 2). University of California-San Francisco performed a propensity score–matched analysis comparing a vHDRB cohort (n = 131) to a HDRB cohort (n = 101). The 10-yr unadjusted biochemical/clinical recurrence-free survival rate was 85.3% for vHDRB and 74.6% for HDRB (p = 0.3). The grade ≥3 GU toxicity rate was 4.6% for vHDRB and 3% for HDRB. The grade ≥3 GI toxicity rate was 2.3% for vHDRB and 0% for HDRB. There was no significant difference in the combined grade ≥3 toxicity rate between the groups [22]. The higher rate of cumulative grade 3 toxicities reported here in comparison to recent prostate SBRT monotherapy trials may be related to the higher allowable bladder dose of 19 Gy to <15 cm^3. The low toxicity rates in PROMETHEUS may be related to the rectal separation, urethral sparing, and detailed organs-at-risk constraints required [13,23,24].

Potential weaknesses of our trial include relatively insensitive baseline staging, which may potentially explain why the majority of relapses occurred at distant sites. PSMA PET staging, which has subsequently been proven to be more sensitive and specific than conventional imagining, was not routinely available for the PROMETHEUS trial; if implemented, it might have screened out some cases with low-volume metastatic disease at baseline, and thus should be part of the standard workup for patients in future studies [25]. We noted two local failures even with the high biological equivalent dose delivered to the whole prostate, suggesting that a microboost to the DIL, as performed in the FLAME trial, may allow further improvements [26]. Such DIL boosting has been investigated with vHDRB, and results demonstrated that this strategy is feasible [27]. A 5-yr follow-up period is insufficient for assessment of longer-term outcomes, and our aim is to collect more mature data in our subsequent phase 3 trial and to link the PROMETHEUS data to registry cohorts to address this issue. Finally, integration of ADT was left to investigator discretion. To improve the therapeutic window, more accurate selection of patients who would benefit from ADT is paramount. In PROMETHEUS, 45% of patients did not receive ADT, which may support an ADT de-escalation strategy. One way to achieve this might be via artificial intelligence assessment of histopathology for intermediate-risk cases, which has shown high predictive power regarding the utility of ADT for such patients [28].

The ultimate validation of vHDRB will be randomised controlled trials with the standard of care as the comparator. Ultrahypofractionated SBRT is an emerging treatment option in the NCCN guidelines, and our preliminary work suggests similar QoL with this approach in comparison to vHDRB [24,29]. The TROG 18.01 NINJA trial is comparing 20 Gy in two fractions followed by 36 Gy in 12 fractions, as tested in PROMETHEUS, versus 40 Gy in five fractions as delivered in PACE B, with the hypothesis that the vHDRB arm allows more flexibility to effectively manage prostate cancers with higher α/β ratios [30]. EORTC PEACE 7 includes a second randomisation to 20 Gy in two fractions as RT dose escalation for patients with high-risk disease initially randomised to addition of darolutamide to long-course ADT and whole-pelvis EBRT (personal communication with Karim Fizazi, August 28, 2023).

5. Conclusions

Our prospective multicentre clinical trial demonstrated an excellent medium-term disease control rate of 94.7% using a vHDRB strategy. The toxicity profile is favourable in comparison to HDRB cohorts. Aspects of this treatment, such as ~12% of men experiencing a subacute flare in GU toxicity at 12–18 mo and ~9% a transient rise in PSA within the first 24 mo, are important for clinicians to appreciate for optimal future management of this patient population. Support for current and future randomised trials of this technique is warranted given these promising results.

Author contributions: Jarad M. Martin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Martin, Sidhom.
Acquisition of data: Pryor, Bucci, Gallagher, Schmidt, Arumugam, Keats, Brown, Glyde.
Analysis and interpretation of data: Wegener, Yeoh, Martin, Greer, Wilton, Richardson.
Drafting of the manuscript: Wegener, Martin.
Critical revision of the manuscript for important intellectual content: Wegener, Martin, Sidhom, Pryor, Bucci.
Statistical analysis: Wegener, Yeoh, Richardson.
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Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2024.01.008.

References

[1] Lloyd T, Hounsome L, Mehay A, Mee S, Verne J, Cooper A. Lifetime risk of being diagnosed with, or dying from, prostate cancer by major ethnic group in England 2008–2010. BMC Med 2015;13:171.

[2] Dayes IS, Parpia S, Gilbert J, et al. Long-term results of a randomized trial comparing iridium implant plus external beam radiation therapy with external beam radiation therapy alone in node-negative locally advanced cancer of the prostate. Int J Radiat Oncol Biol Phys 2017;99:90–3.

[3] Hoskin PJ, Rojas AM, Ostler PJ, Bryant L, Lowe GJ. Randomised trial of external-beam radiotherapy alone or with high-dose-rate brachytherapy for prostate cancer: mature 12-year results. Radiother Oncol 2021;154:214–9.

[4] Morris WJ, Tyldesley S, Rodda S, et al. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98:275–85.

[5] Roberts MJ, Papa N, Perera M, et al. A contemporary, nationwide analysis of surgery and radiotherapy treatment for prostate cancer. BJU Int 2019;124(Suppl 1):31–6.

[6] Gomez-Iturriaga A, Keyes M, Martin J, Spratt DE. Should brachytherapy be added to external beam radiotherapy for prostate cancer? Lancet Oncol 2022;23:23–5.

[7] Keall P, Nguyen DT, O'Brien R, et al. Real-time image guided ablative prostate cancer radiation therapy: results from the TROG 15.01 SPARK trial. Int J Radiat Oncol Biol Phys 2020;107:530–8.

[8] Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet 2019;394:385–95.

[9] Tree AC, Ostler P, van der Voet H, et al. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2022;23:1308–20.

[10] van As N, Tree A, Patel J, et al. 5-Year outcomes from PACE B: an international phase III randomized controlled trial comparing stereotactic body radiotherapy (SBRT) vs. conventionally fractionated or moderately hypo fractionated external beam radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2023;117:4.e2–e3.

[11] Rodda S, Tyldesley S, Morris WJ, et al. ASCENDE-RT: an analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98:286–95.

[12] Wegener E, Samuels J, Sidhom M, et al. Virtual HDR boost for prostate cancer: rebooting a classic treatment using modern tech. Cancers 2023;15:2018.

[13] Richardson M, Sidhom M, Gallagher S, et al. Prostate Multicentre External beam Radiotherapy Using a Stereotactic Boost: the PROMETHEUS study protocol. BMC Cancer 2018;18:588.

[14] Pryor D, Sidhom M, Arumugam S, et al. Phase 2 multicenter study of gantry-based stereotactic radiotherapy boost for intermediate and high risk prostate cancer (PROMETHEUS). Front Oncol 2019;9:217.

[15] Legge K, Nguyen D, Ng JA, et al. Real-time intrafraction prostate motion during linac based stereotactic radiotherapy with rectal displacement. J Appl Clin Med Phys 2017;18:130–6.

[16] Arumugam S, Sidhom M, Xing A, Holloway L. An online X-ray based position validation system for prostate hypofractionated radiotherapy. Med Phys 2016;43:961–74.

[17] Godoy G, Chong KT, Cronin A, et al. Extent of pelvic lymph node dissection and the impact of standard template dissection on nomogram prediction of lymph node involvement. Eur Urol 2011;60:195–201. https://doi.org/10.1016/j.eururo.2011.01.016.

[18] Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the Expanded Prostate Cancer Index Composite instrument for measuring health-related quality of life among prostate cancer survivors. Urology 2010;76:1245–50.

[19] Sandra M, Wei J, Litwin M. Scoring instructions for the Expanded Prostate Cancer Index Composite short form (EPIC-26). Ann Arbor, MI: University of Michigan; 2002.

[20] Roach 3rd M, Hanks G, Thames Jr H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965–74.

[21] Pasquier D, Nickers P, Peiffert D, et al. A multicenter phase 2 study of ultrahypofractionated stereotactic boost after external beam radiotherapy in intermediate-risk prostate carcinoma: a very long-term analysis of the CKNO-PRO trial. Eur Urol Open Sci 2023;54:80–7.

[22] Chen WC, Li Y, Lazar A, et al. Stereotactic body radiation therapy and high-dose-rate brachytherapy boost in combination with intensity modulated radiation therapy for localized prostate cancer: a single-institution propensity score matched analysis. Int J Radiat Oncol Biol Phys 2021;110:429–37.

[23] Wilton L, Richardson M, Keats S, et al. Rectal protection in prostate stereotactic radiotherapy: a retrospective exploratory analysis of two rectal displacement devices. J Med Radiat Sci 2017;64:266–73.

[24] Richardson M, Sidhom M, Keall P, et al. Genitourinary quality-of-life comparison between urethral sparing prostate stereotactic body radiation therapy monotherapy and virtual high-dose-rate brachytherapy boost. Int J Radiat Oncol Biol Phys 2023;116:1069–78.

[25] Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020;395:1208–16.

[26] Groen VH, Haustermans K, Pos FJ, et al. Patterns of failure following external beam radiotherapy with or without an additional focal boost in the randomized controlled FLAME trial for localized prostate cancer. Eur Urol 2022;82:252–7.

[27] Eade T, Hruby G, Booth J, et al. Results of a prospective dose escalation study of linear accelerator-based virtual brachytherapy (BOOSTER) for Prostate Cancer; Virtual HDR Brachytherapy for Prostate Cancer. Adv Radiat Oncol. 2019;4:623–30.

[28] Spratt DE, Tang S, Sun Y, et al. Artificial intelligence predictive model for hormone therapy use in prostate cancer. Res Sq. Preprint. https://doi.org/10.21203/rs.3.rs-2790858/v1.

[29] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): prostate cancer v.1.2023.

[30] Martin J, Keall P, Siva S, et al. TROG 18.01 phase III randomised clinical trial of the novel integration of new prostate radiation schedules with adjuvant androgen deprivation: NINJA study protocol. BMJ Open 2019;9:e030731.