Physics and Imaging in Radiation Oncology 32 (2024) 100645

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/physics-and-imaging-in-radiation-oncology

Review Article

A review of whole gland prostate brachytherapy with focal dose escalation to intra-prostatic lesions: Clinical efficacy and technical aspects

Joel Poder [a,b,c,*], Peter Hoskin [d,e], Hayley Reynolds [f], Tsz Him Chan [f], Annette Haworth [c]

[a] St George Hospital Cancer Care Centre, Kogarah, NSW, Australia
[b] Centre for Medical Radiation Physics, University of Wollongong, Wollongong, NSW, Australia
[c] School of Physics, University of Sydney, Camperdown, NSW, Australia
[d] Mount Vernon Cancer Centre, Northwood, United Kingdom
[e] Division of Cancer Sciences, University of Manchester, United Kingdom
[f] Auckland Bioengineering Institute, The University of Auckland, Auckland, New Zealand

ARTICLE INFO

Keywords:
Brachytherapy
Intra-prostatic lesion
Prostate
Dose escalation

ABSTRACT

Focal boost to intra-prostatic lesions (IPLs) in radiotherapy could enhance treatment efficacy. Brachytherapy (BT), delivering highly conformal dose with sharp dose gradients emerges as a potentially optimal approach for precise dose escalation to IPLs. This study aims to consolidate clinical and planning studies that implemented whole gland prostate BT and focal dose escalation to IPLs, with the view to synthesize evidence on the strategy's effectiveness and variability. In this review, we identified nine clinical studies and ten planning/simulation studies focusing on whole gland prostate BT with IPL dose escalation. From the clinical studies, the use of whole gland prostate BT with focal dose escalation in combination with external beam radiotherapy (EBRT) appears to be a safe and effective 21 form of treatment for men with T1b – T2c prostate cancer with average five-year biochemical failure22 free survival (BFFS) of 94 % (range 81.1 %–100 %) and minimal grade three toxicities reported. Both clinical and planning studies exemplified the high level of focal dose escalation achievable using BT with a mean IPL D90 % of 132 % and 146 %, respectively (expressed as a % of the whole gland prescription dose). There was considerable variation in the reporting of clinical and technical data in the identified studies. To facilitate a more widespread and uniform adoption of the technique, recommendations on essential and desirable items to be included in future studies incorporating whole gland prostate BT with focal boost to IPLs are provided.

1. Introduction

Prostate cancer (PCa) ranks as the second most prevalent cancer in males globally, with projections estimating around 2.3 million new cases and 740,000 fatalities by the year 2040 [1,2]. Radiotherapy is a cornerstone in PCa management, yet traditional approaches, which prescribe uniform dose distributions, fail to address the condition's multifocal nature and the heterogeneity present both within and between tumours [3,4]. Research has shown that post-radiotherapy local recurrences in the prostate often emerge from the sites of the original tumours [5,6]. This has led to the proposition that incorporating patient-specific biological data into treatment planning could allow for the strategic targeting of higher doses to areas at greater risk, thereby improving tumour control [7].

Incorporating a focal boost to the macroscopic tumour volume as defined on multi-parametric magnetic resonance imaging (mpMRI) or prostate specific membrane antigen (PSMA) positron emission tomography (PET) scans into whole gland prostate radiotherapy could enhance treatment efficacy. These macroscopic tumour volumes are referred to as intra-prostatic lesions (IPLs). Using this approach IPLs may be defined as additional clinical target volumes (IPL CTVs) and prescribed an escalated dose, relative to the prostate gland CTV.

The FLAME trial, a phase III, multicentre, randomized study, showed an improved 5 year prostate-specific antigen (PSA)-relapse-free survival (92 %) in patients receiving an external beam radiotherapy (EBRT) boost to the IPL compared to no boost (85 %) [8]. The trial also showed a correlation between the dose received by the IPL and the PSA-relapse-free survival [8]. Brachytherapy (BT), delivering highly conformal

* Corresponding author at: St George Hospital Cancer Care Centre, Kogarah, NSW, Australia.
E-mail address: Joel.Poder@health.nsw.gov.au (J. Poder).

https://doi.org/10.1016/j.phro.2024.100645
Received 25 April 2024; Received in revised form 22 August 2024; Accepted 9 September 2024
Available online 16 September 2024

dose distributions with sharp dose gradients is therefore well placed to be the optimal approach for precise dose escalation to IPLs, especially when combined with external beam radiotherapy (EBRT) for treating high-risk prostate cancer [9–15].

This review article assesses evidence for the role of brachytherapy for whole gland prostate radiotherapy with dose escalation to the IPL in planning and clinical studies. It delves into the clinical results from focal boost trials, methodologies employed for IPL identification, treatment planning strategies, dosimetric outcomes reported, constraints related to dose escalation, and the ongoing challenges as well as future opportunities faced in BT focal boost implementation.

2. Methods

2.1. Eligibility criteria

This review and analysis were reported according to the guidelines provided in the PRISMA statement. We included clinical and planning studies of whole gland prostate brachytherapy treatments with dose escalation to IPLs.

2.2. Search strategy and study selection process

Literature searches were conducted in March 2024 through a search of the Cochrane Library, EMBASE, and MEDLINE electronic databases. The data of coverage was restricted to 2000 onwards and searches were limited to English language only. The search was conducted using a combination of subject headings and keywords: ("Boost brachytherapy" OR "prostate brachytherapy" OR "LDR boost" OR "HDR boost") AND (prostate OR "prostate cancer" OR"). Additionally, references of included studies were manually analysed to search for any additional studies. Duplicates of identified studies were removed prior to screening. For the clinical studies, only the primary publications were included.

3. Results

3.1. Clinical effectiveness of intra-prostatic dose escalation with brachytherapy

Table 1 provides a summary of the clinical studies focusing on IPL dose escalation using BT. There were 9 studies identified that reported oncological outcomes and/or toxicities of the technique. The studies varied in their application of BT and the patient cohorts treated, with 6/9 incorporating a combination of BT and external beam radiotherapy (EBRT) in a primary treatment setting, and 3/9 utilising BT alone in a primary treatment setting.

Of the studies examining the use of combined BT and EBRT (6/9), the average median follow-up was 51 months (range 18 – 71), and average 5-year biochemical failure-free survival (BFFS) was 94 % (range 81.1 %−100 %). In terms of acute toxicities, the studies by Vigneault et al. [12], Guimond et al. [16], and Sanmemed et al. [14] reported acute grade 3 genito-urinary (GU) toxicities at a rate of 5 %, 0.2 %, and 2.5 %, respectively. Strnad et al. [17] reported 4 % grade 3 late GU toxicity. The two remaining studies [10,11] reported ≤ grade 2 acute GU and ≤ grade 1 or 2 gastrointestinal (GI) toxicities. A major limitation of these studies however is that each of them were single institution and retrospective in nature, patient numbers were limited (range 8–101), and the patient reported outcome measures were not collected.

Three studies included in Table 1 report on the use of IPL dose escalation using BT as a monotherapy. Two of the three studies delivered a single fraction of high dose rate (HDR) BT as a monotherapy and reported 5-year BFFS of 68.7 % [18] and 76 %–88 % [19]. The study by Armstrong et al. [19] performed dose de-escalation to non-IPL prostate tissue. Both studies conclude that single fraction HDR BT monotherapy is inferior to fractionated techniques for this patient cohort despite the IPL dose escalation achieved, and that single fraction HDR BT monotherapy should not be used outside the confines of a clinical trial. Ennis et al. [20] reported on a phase I/II study of low dose rate (LDR) BT dose de-escalation to non-IPL prostate tissue with a median follow-up of only 31.5 months and 2-year BFFS of 100 %. Only Alayed et al.[18] reported 5 % grade 3 toxicities, with all other toxicities reported by studies investigating IPL dose escalation with BT as a monotherapy being ≤ grade 2.

The use of BT with focal dose escalation in combination with EBRT appears to be a safe and effective form of treatment for men with T1b – T2c prostate cancer. Larger, multi-institutional studies are required to confirm the safety and BFFS benefit of focal dose escalation over single whole gland CTV BT prescriptions. In the setting of focal dose escalation using BT in a monotherapy setting for either de novo or salvage treatment, the question of its efficacy in a LDR and fractionated HDR treatments remains unanswered, however the use of HDR BT monotherapy with or without focal IPL dose escalation should be used in the setting of a clinical trial.

3.2. Technical and dosimetric data reported in clinical and planning studies utilising brachytherapy for intra-prostatic dose escalation

3.2.1. Imaging modalities utilised

The technical and dosimetric data reported in the 9 clinical studies summarised given in Table 2 and for the planning studies in Table 3. The most common modality (6/9) used for IPL identification in the clinical studies was magnetic resonance imaging (MRI) via multi-parametric MRI (mpMRI) alone or in combination with MRI-spectroscopy (MRS). The remaining studies used either sextant biopsies to guide dose escalation [16] or utilised *trans*-rectal ultrasound (TRUS) [17,20]. TRUS was the most common imaging modality used for treatment planning (6/9), followed by MRI (2/9), and CT (1/9).

This trend is also observed in Table 3 for the planning studies where all 10 studies utilised mpMRI either alone (8/10), in combination with MRSI (1/10), or prostate-specific membrane antigen (PSMA) positron emission tomography (PET) (1/10). TRUS was again the most common modality used for treatment planning (8/10), followed by CT (1/10) and a combination of MRI/CT (1/10). The predominant use of TRUS as the treatment planning image dataset reflects the wider trend within the prostate brachytherapy field where TRUS is recommended for use as the primary dataset in both HDR and LDR prostate brachytherapy [21]. The use of MRI, specifically mpMRI to identify IPLs in these studies is also reflective of the radiotherapy community in general [22]. However, the benefit of PSMA PET either alone, or in conjunction with mpMRI in this setting is a growing area of research [23–25] and may be investigated further in future studies involving the use of BT for focal dose escalation to IPLs.

3.2.2. Use of image registration techniques

A key component of IPL dose escalation in radiotherapy is propagation of IPL contours to treatment planning image datasets. From Table 2, the methods used for image registration in clinical brachytherapy IPL dose escalation studies vary considerably. Amongst these studies only 7/9 reported on the type of image registration used. Amongst those that did report their methodology, rigid image registration was the most common (3/10), followed by deformable image registration (1/10), and affine based registration (1/10). The remainder (2/10) utilised the same dataset for identification of IPL and for treatment planning, and therefore image registration was not required.

All 10 planning studies reported the type of image registration used, again rigid image registration was the most popular (7/10), followed by deformable image registration (3/10). Future clinical studies involving the use of focal dose escalation to IPLs with BT should report on the image registration technique used. The preference for rigid image registration over deformable image registration in these studies may be due to the difficulties in performing deformable image registration in

Table 1
Reported clinical outcomes for clinical studies utilising intra-prostatic boost using brachytherapy. GU=genitourinary, GI=gastrointestinal, HDR=high dose rate, EBRT=external beam radiotherapy, LDR=low dose rate, BT=brachytherapy, Gy = Gray, BFFS=biochemical failure free survival, IPL=intra-prostatic lesion.

Study	Number of participants	Risk group	Dose prescription	Median Follow-up	Oncological outcome (s)	Acute GU toxicity	Acute GI toxicity	Late GU toxicity	Late GI toxicity
Vigneault et al. 2016 [12]	19	T1c = 58 %% T2a = 26 % T2b = 10 % T2c = 6 %%	46 Gy/23 EBRT+15 Gy/1 HDR BT	62 months	5 year BFFS=94.7 %	5 % grade 3	≤grade 1	≤grade 2	≤grade 1
Chapman et al. 2018 [11]	8	T2a = 50 % T2b = 12.5 % T3a = 25 % T3b = 12.5 %	45 Gy/25 EBRT+19 Gy/2 HDR BT	59 months	5 year BFFS=100 %	≤grade 2	≤grade 1	≤grade 2	≤grade 1
Guimond et al. 2019 [16]	55	T1c = 51 % T2a = 24 % T2b = 25 %	46 Gy/23 EBRT+110 Gy LDR BT	71 months	7 year BFFS=96 %	≤grade 2	≤grade 1	0.2 % grade 3	≤grade 1
Alayed et al. 2021 [18]	60	T1c = 0 % T2a = 48 % T2b = 23 % T2c = 29 %	19 Gy/1 HDR BT	50 months	5 year BFFS=68.7 %	Not reported	Not reported	≤grade 2	5 % grade 3
Gomez-Iturriaga 2016 [10]	15	T1c = 67 % T2a = 27 % T2b = 6 %	37.5 Gy/15 EBRT+15 Gy/1 HDR	18 months	Not reported	≤ grade 2	≤ grade 2	≤ grade 2	≤ grade 1
Strnad et al. 2022 [17]	101	T1 = 33.7 % T2 = 58.4 % T3 = 7.9 %	50.4 Gy/28 EBRT+35 Gy/2 PDR	65 months	5 year BFFS=98.1 % (low/intermediate) 81.% (high)	Not reported	Not reported	4 % grade 3	≤ grade 1
Sanmamed et al. (compared HDR with EBRT) 2020 [14]	40	T1c = 67 % T2a = 27 % T2b = 3 % T2c = 3 %	76 Gy/38 EBRT+10 Gy/1 HDR to IPL	31 months	Not reported	2.5 % grade 3	≤grade 1	≤grade 2	≤grade 1
Armstrong et al. 2021 [19]	50	T1c = 4 % T2a = 24 % T2b = 20 % T2c = 44 % T3a = 8 % T1c = 0 % T2a = 44 % T2b = 4 % T2c = 32 % T3a = 20 %	19 Gy/1 HDR BT Group 1 = 65–75 % 19 Gy to non-IPL Group 2 = <50 % 19 Gy to non-IPL	75 months / 57 months	5 year BFFS=88 % (group 1) and 76 % (group 2)	≤ grade 2	≤ grade 1	≤ grade 2	≤ grade 1

(*continued on next page*)

Table 1 (*continued*)

Study	Number of participants	Risk group	Dose prescription	Median Follow-up	Oncological outcome (s)	Acute GU toxicity	Acute GI toxicity	Late GU toxicity	Late GI toxicity
Ennis et al. (LDR) 2015 [20]	13	T1c = 76.9 % T2a = 7.7 % T2b = 15.4 %	145 Gy with normal prostate de-escalation	31.5 months	2 year BFFS=100 %	≤grade 2	≤grade 1	≤grade 2	≤grade 1

Table 2
Reported technical and dosimetric data for clinical studies utilising intra-prostatic boost using brachytherapy. HDR=high dose rate, EBRT=external beam radiotherapy, LDR=low dose rate, mpMRI=multi-parametric magnetic resonance imaging, MRS=magnetic resonance spectroscopy, TRUS=*trans*-rectal ultrasound, MRI=magnetic resonance imaging, CT=computed tomography, IPL=intra-prostatic lesion.

Study	Number of participants	Modality for IPL identification	Modality for treatment planning	Image registration method	Reported image registration uncertainty (mm)	IPL margin size (mm)	Reported dose to IPL(s)
Vigneault et al. 2016 [12]	19	mpMRI/MRS	TRUS	Not reported	Not reported	0	Mean V120% = 95.9 %
Chapman et al. 2018 [11]	8	mpMRI/MRS	CT	Rigid image registration	2	0	Median D90% = 132 % Median V120% = 100 %
Guimond et al. 2019 [16]	55	Sextant biopsy	TRUS	N/A	N/A	0	Median V100% = 100 % Median V150% = 91.2 %
Alayed et al. 2021 [17]	60	mpMRI	TRUS	Affine based registration	Not reported	0	Median D90% = 147 %
Gomez-Iturriaga 2016 [10]	15	mpMRI/MRS	TRUS	Rigid image registration	Not reported	Not reported	Median D90% = 142.7 % Median V150% = 78.8 %
Strnad et al. 2022 [18]	101	TRUS HistoScanning	TRUS	Rigid image registration	0	0	Mean D90% = 125 % Medan V150% = 60.2 %
Sanmamed et al. (compared HDR with EBRT) 2020 [14]	40	mpMRI	MRI	Deformable image registration – biomechanical	Not reported	1–2 mm	N/A
Armstrong et al. 2021 [19]	50	mpMRI	MRI	Not reported	Not reported	2 mm	N/A
Ennis et al. (LDR) 2015 [20]	13	Ultrasound tissue type imaging	TRUS	None	0 mm	0 mm	Not reported

multi-modality images [26], the limitations of deformable image registration algorithms in the presence of brachytherapy needles/catheters [27], or the lack of advanced image registration algorithms in brachytherapy treatment planning software [28]. Use of deformable image registration in this setting may however be advantageous, particularly when co-registering image sets with and without ultrasound probes in the rectum [26]. An optimal approach to this process would utilise functional imaging (mpMRI or PSMA PET) collected at a timepoint close to the BT procedure, fused within the BT treatment planning system using deformable image registration prior to needle implant to optimise needle placement in order to dose escalation to IPLs. However, care must be taken to ensure appropriate deformation of the prostate internal anatomy when utilising such a technique, since this can only be achieved through the use of a robust commissioning process and patient specific quality assurance testing, utilising tools such as the Jacobian index and inverse consistency [29].

The uncertainty in the image registration method utilised should inform the use of a margin around the IPL contour used to direct the escalated dose within the prostate. Amongst the clinical studies only 3/9 reported the uncertainty in their image registration method, the magnitude of which ranged from 0 mm to 2 mm. Planning studies were more likely to report on image registration uncertainty (7/10) with values ranging from 0.5 mm to 4.5 mm. Future studies focussing on IPL focal dose escalation utilising BT should report on the uncertainty of image registration in their methods.

3.2.3. *Intra-prostatic lesion margins*

From Table 2 and Table 3, the use of a margin around identified IPLs also varies across the clinical and planning studies. Only 2/19 of the studies included in Tables 2 and 3 did not report on the margin size used. Of the clinical studies, a 0 mm margin was most commonly used (5/9), followed by 1–2 mm (1/10) and 2 mm (3/10). In the planning studies a 0 mm margin was again most common (3/10) along with a 2 mm margin (3/10), followed by 4.5 mm (2/10), and 1.5 mm (1/10). Margin size appears to correlate with the magnitude of the reported image registration uncertainty. The benefit of expanding IPL contours in focal dose escalation studies in BT remains a contentious topic. Since non-IPL prostatic tissue surrounding the IPL is likely to also receive an escalated dose by nature of the pattern of dose distributions in prostate brachytherapy, there is likely to exist an inherent dosimetric margin around the IPL. A 0 mm margin around the IPL may be appropriate if the uncertainties in delineating the IPL are consistent with the dose gradient

Table 3
Reported technical and dosimetric data for planning studies utilising intra-prostatic boost using brachytherapy. LDR=low dose rate, HDR=high dose rate, mpMRI=multi-parametric magnetic resonance imaging, TRUS=*trans*-rectal ultrasound, MRI=magnetic resonance imaging, CT=computed tomography, IPL=intra-prostatic lesion, PSMA PET=prostate-specific membrane antigen positron emission tomography.

Study	Number of patients included	Modality for IPL identification	Modality for treatment planning	Image registration method	Reported image registration uncertainty (mm)	IPL margin size (mm)	Reported dose to IPL(s)
Wang et al. 2019 [13]	17	mpMRI	CT	Deformable image registration – b-spline	2	2	Mean D90% = 164.5 %
Mason et al. 2015 [31]	16	mpMRI	TRUS	Rigid image registration	4.2	4.5	Median D90% = 139 %, Median V150% = 77.2 %
Mason et al. 2014 [30]	15	mpMRI	TRUS	Rigid image registration	4.2	4.5	Median D90% = 139 % Median V150% = 70.9 %
Carlone et al. 2016 [44]	10	mpMRI	TRUS	Deformable image registration – biomechanical	Not reported	2	Mean D95% = 136.3 %
Crook et al. 2014 [9]	26	mpMRI	TRUS	Rigid image registration	1 mm	0	Median D90% = 131 % Median V125% = 96.1 %
Clark et al. 2023 (LDR) [45]	20	mpMRI	TRUS	Rigid image registration	Not reported	Sector based contouring	Median D90% = 159 % Median V150% = 99 %
Luminais et al. 2022 [46]	24	mpMRI	TRUS	Rigid image registration	Not reported	Not reported	Mean D90% = 155 %
Tissaverasinghe et al. (LDR & HDR) 2019 [47]	60	mPMRI	TRUS	Rigid image registration	1	0	LDR Mean D90% = 151 % HDR Mean D90% = 132 %
Poder et al. 2023 [28]	20	mpMRI+PSMA PET	TRUS	Deformable image registration – contour based	0.5 mm	2 mm	Mean D98% = 135 %
Pouliot et al. 2004 [48]	10	mpMRI/MRSI	MRI/CT	Rigid image registration	1.5 mm	0 mm	Mean V150% = 86.1 %

surrounding it and may be necessary when the IPL is immediately adjacent to an anatomical boundary such as the prostate capsule (assuming no extra-prostatic extension) or the urethra.

3.2.4. *Level of intra-prostatic lesion dose escalation achieved*

The image registration uncertainty, and ultimately the IPL margin size used may also affect the ability of the treatment planning system to maximise the dose to the IPL. The achievable level of focal dose escalation to IPLs is dependent on a complex relationship between the size of the IPL (which increases with margin size), and the proximity of the IPL to nearby organs at risk such as the urethra and rectum [28]. Comparison of the level of dose escalation achieved across the studies summarised in Table 2 and Table 3 proves difficult due to the variation on reported dosimetric parameters (e.g. D90%, V150%, D98%, and V100%). However, for the studies that reported the IPL D90%, the clinical studies in Table 2 (n = 5) reported a mean value of 132 % (range 118 %–147 %). The planning studies in Table 3 (n = 7) reported a mean D90% of 146 % (range 131 %–164.5 %).

Due to the limited number of studies reporting the same dose metric, comparison of the clinical and planning studies is not appropriate, however there does appear to be a trend for higher levels of dose escalation achieved in the planning studies in Table 3 compared to the clinical studies in Table 2. This may be due to the differences in treatment planning techniques used between the studies. For example, the studies by Wang et al. [13], Mason et al. [30,31], and Poder et al. [28] assumed knowledge of the IPL locations at the time of catheter insertion in the form of a contour. These studies therefore allowed the addition of catheters in their planning studies placed directly through the IPL contours, ensuring maximum dose escalation, and demonstrating the advantage of BT in this setting. By utilising such a technique in future clinical studies involving BT for focal dose escalation to IPLs, clinician confidence in further escalation of dose may be improved.

The number of IPLs present, their volume, and position relative to organs at risk may also have a significant impact on the level of dose escalation that can be achieved. Few studies included in this review reported the number, volume, and position of IPLs. This information should be reported in future studies to allow for a more comprehensive comparison between techniques used to perform focal dose escalation to IPLs.

The FLAME study [8] demonstrated a positive correlation between the escalated dose received by the IPLs and BFFS at 5 years. Studies utilising EBRT to achieve this dose escalation have reported median IPL V100% doses of 126 % [22]. Similarly, in hypo-FLAME, IPLs were delivered a mean escalated dose of 115 % of the prescribed dose to the prostate [32]. This suggests that, with their inherent dose gradients BT may allow increased IPL dose escalation, and therefore improve BFFS as compared to EBRT. Further confirmatory studies in the form of multi-institutional clinical trials are warranted in this setting.

4. Discussion

Table 4 provides a proposed list of items that should be reported as

Table 4
Recommended items to be included for future clinical and planning studies incorporating IPL focal dose escalation using BT. IPL=intra-prostatic lesion. CTV=clinical target volume. PTV=planning target volume.

	Essential	Desirable
Clinical	• Number of patients included. • Inclusion/exclusion criteria. Follow-up length. • Oncological outcomes. • Early/late toxicities. • Number, volume, and location of IPLs per patient.	• Patient reported outcome measures. • Quality of life. • Recruiting period.
Imaging/ contouring	• Image type used for treatment planning. Image type used for contouring. • IPL contouring instructions. • IPL & prostate CTV-PTV margin description Prostate/OAR contouring instructions. • Image registration methodology. • Image registration uncertainty.	• Treatment planning image spatial resolution. • IPL contouring image spatial resolution.
Treatment planning/ dosimetry	• Prescription dose and CTV/PTV dose coverage goals and achieved metrics (V100%, D90%, D98%, V150%, mean dose). • Organ at risk dose constraints and achieved dose metrics. • Brachytherapy source type.	• Dose calculation algorithm. • Dose calculation grid size. • Number of needles implanted. • Total reference air-kerma.

part of clinical and planning studies incorporating BT for focal dose escalation to IPLs. Inclusion of these items will facilitate a more reproducible approach to IPL focal dose escalation using BT in future studies.

The challenges of image registration have been discussed in depth throughout this review, however, the process of identifying the IPL volumes on mpMRI and/or PSMA-PET also presents a significant challenge. The inter-observer contouring variability in defining IPLs has been well-documented, with numerous studies showing that not only is inter-observer contouring variability poor on both mpMRI and PSMA-PET [28,33,34], but also that inter-modality agreement between IPLs identified on mpMRI and PSMA-PET is limited [26,33]. These uncertainties should also be considered when performing focal dose escalation to IPLs using prostate brachytherapy.

Traditional methods of prostate radiotherapy have used a single CTV encompassing the entire prostate gland. Focal dose escalation to IPLs represents the next logical step by escalating dose to regions of prostatic tissue that are known to be the most likely site of disease recurrence [35]. Following these traditional methods of a single whole gland CTV, the use of HDR or LDR BT in combination with EBRT has been shown to be more effective in biochemical control of prostate cancer relative to EBRT alone [35,36]. However, in the case of LDR BT, rates of grade 3 toxicity (in particular GU toxicities) have been interpreted unacceptably high [37]. Consequently, there may be a future opportunity in the form of a clinical trial to de-escalate dose to the non-IPL prostatic tissue in order to limit the rates of GU and GI toxicities further, whilst still maintaining acceptable rates of biochemical control. Whilst this approach was not successful in the single fraction prostate BT monotherapy setting [18,19], it is yet to be explored in fractionated monotherapy, or combination BT and EBRT setting.

In this review we have identified clinical and planning studies that demonstrate BT provides an effective method for dose escalation with, in most cases, acceptable or reduced toxicity compared with EBRT. Further increasing the therapeutic window, that is, increasing tumour control with reduced toxicity may not be possible with the current dose prescription method. In contrast to the current dose prescription approach, a voxel-wise, biologically targeted dose prescription method has shown potential for modulating the dose within the prostate [38]. In silico EBRT studies have demonstrated improved tumour control probability without increasing toxicity [22,39]. This approach requires a voxel-wise dose prescription based on a spatial map of tumour biology, which can be derived from mpMRI [38,40,41] and incorporate PSMA PET/CT when available [42]. In the case of BT, defining a region of hypoxia for example [43], would guide optimal needle placement within the IPL. Such an approach would utilize the inherent heterogeneous nature of BT dose distributions.

In conclusion, dose deposition characteristics of BT make it an attractive option for focal dose escalation to IPLs, as shown in the clinical and planning studies included as part of this review. Further, the use of BT for focal dose escalation to IPLs has shown promise with favourable BFFS and low toxicity in the limited number of single institution clinical trials reported to date. To confirm the efficacy of the technique, larger multi-institutional clinical trials are required. Future clinical and planning studies would benefit from a detailed, and uniform reporting methodology to allow for a more comprehensive comparison between studies and to facilitate widespread adoption of the technique.

CRediT authorship contribution statement

Joel Poder: Conceptualization, Data curation, Investigation, Writing – original draft. **Peter Hoskin:** Supervision, Writing – review & editing. **Hayley Reynolds:** Supervision, Writing – review & editing. **Tsz Him Chan:** Writing – review & editing. **Annette Haworth:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent global patterns in prostate cancer incidence and mortality rates. Eur Urol 2020;77:38–52. https://doi.org/10.1016/j.eururo.2019.08.005.
[2] Observatory GC. International Agency for Research on Cancer 2020. Cancer Today 2020.
[3] Opell M, Zeng J, Bauer J, Connelly R, Zhang W, Sesterhenn I, et al. Investigating the distribution of prostate cancer using three-dimensional computer simulation. Prostate Cancer P D 2002;5:204–8. https://doi.org/10.1038/sj.pcan.4500577.
[4] Greene DR, Fitzpatrick JM, Scardino PT. Anatomy of the prostate and distribution of early prostate cancer. Semin Surg Oncol: Wiley Online Library 1995:9–22. https://doi.org/10.1002/ssu.2980110104.
[5] Pucar D, Hricak H, Shukla-Dave A, Kuroiwa K, Drobnjak M, Eastham J, et al. Clinically significant prostate cancer local recurrence after radiation therapy occurs at the site of primary tumor: magnetic resonance imaging and step-section pathology evidence. Int J Radiat Oncol 2007;69:62–9. https://doi.org/10.1016/j.ijrobp.2007.03.065.
[6] Arrayeh E, Westphalen AC, Kurhanewicz J, Roach III M, Jung AJ, Carroll PR, et al. Does local recurrence of prostate cancer after radiation therapy occur at the site of primary tumor? Results of a longitudinal MRI and MRSI study. Int J Radiat Oncol 2012;82:e787–93. https://doi.org/10.1016/j.ijrobp.2011.11.030.
[7] Her E, Haworth A, Reynolds H, Sun Y, Kennedy A, Panettieri V, et al. Voxel-level biological optimisation of prostate IMRT using patient-specific tumour location and clonogen density derived from mpMRI. Radiat Oncol 2020;15:1–13. https://doi.org/10.1186/s13014-020-01568-6.
[8] Kerkmeijer LG, Groen VH, Pos FJ, Haustermans K, Monninkhof EM, Smeenk RJ, et al. Focal boost to the intraprostatic tumor in external beam radiotherapy for patients with localized prostate cancer: results from the FLAME randomized phase III trial. J Clin Oncol 2021;39(7):787–96. https://doi.org/10.1200/JCO.20.02873.
[9] Crook J, Ots A, Gaztañaga M, Schmid M, Araujo C, Hilts M, et al. Ultrasound-planned high-dose-rate prostate brachytherapy: dose painting to the dominant intraprostatic lesion. Brachytherapy 2014;13:433–41. https://doi.org/10.1016/j.brachy.2014.05.006.
[10] Gomez-Iturriaga A, Casquero F, Urresola A, Ezquerro A, Lopez JI, Espinosa JM, et al. Dose escalation to dominant intraprostatic lesions with MRI-transrectal ultrasound fusion high-dose-rate prostate brachytherapy. Prospective phase II trial. Radiother Oncol 2016;119:91–6. https://doi.org/10.1016/j.radonc.2016.02.004.
[11] Chapman CH, Braunstein SE, Pouliot J, Noworolski SM, Weinberg V, Cunha A, et al. Phase I study of dose escalation to dominant intraprostatic lesions using high-dose-rate brachytherapy. J Contemp Brachyther 2018;10:193–201. https://doi.org/10.5114/jcb.2018.76881.
[12] Vigneault E, Mbodji K, Racine L-G, Chevrette E, Lavallée M-C, Martin A-G, et al. Image-guided high-dose-rate brachytherapy boost to the dominant intraprostatic

lesion using multiparametric magnetic resonance imaging including spectroscopy: results of a prospective study. Brachytherapy 2016;15:746–51. https://doi.org/10.1016/j.brachy.2016.09.004.
[13] Wang T, Press RH, Giles M, Jani AB, Rossi P, Lei Y, et al. Multiparametric MRI-guided dose boost to dominant intraprostatic lesions in CT-based High-dose-rate prostate brachytherapy. Brit J Radiol 2019;92:20190089. https://doi.org/10.1259/bjr.20190089.
[14] Sanmamed N, Lee J, Berlin A, Craig T, Lao B, Rink A, et al. Tumor-targeted dose escalation for localized prostate cancer using MR-guided HDR brachytherapy (HDR) or integrated VMAT (IB-VMAT) boost: Dosimetry, toxicity and health related quality of life. Radiother Oncol 2020;149:240–5. https://doi.org/10.1016/j.radonc.2020.05.029.
[15] Oh J, Tyldesley S, Pai H, McKenzie M, Halperin R, Duncan G, et al. An updated analysis of the survival endpoints of ASCENDE-RT. Int J Radiat Oncol 2023;115:1061–70. https://doi.org/10.1016/j.ijrobp.2022.11.005.
[16] Guimond E, Lavallée M-C, Foster W, Vigneault É, Guay K, Martin A-G. Impact of a dominant intraprostatic lesion (DIL) boost defined by sextant biopsy in permanent I-125 prostate implants on biochemical disease free survival (bDFS) and toxicity outcomes. Radiother Oncol 2019;133:62–7. https://doi.org/10.1016/j.radonc.2018.12.027.
[17] Strnad V, Lotter M, Kreppner S, Fietkau R. Brachytherapy focal dose escalation using ultrasound based tissue characterization by patients with non-metastatic prostate cancer: five-year results from single-center phase 2 trial. Brachytherapy 2022;21:415–23. https://doi.org/10.1016/j.brachy.2022.02.003.
[18] Alayed Y, Loblaw A, McGuffin M, Chung HT, Tseng C-L, D'Alimonte L, et al. Single-fraction HDR brachytherapy as monotherapy in low and intermediate risk prostate cancer: outcomes from two clinical trials with and without an MRI-guided boost. Radiother Oncol 2021;154:29–35. https://doi.org/10.1016/j.radonc.2020.09.007.
[19] Armstrong S, Brown S, Stancliffe M, Ostler P, Hughes R, Hoskin P, et al. Single dose high-dose-rate brachytherapy with focal dose escalation for prostate cancer: mature results of a phase 2 clinical trial. Radiother Oncol 2021;159:67–74. https://doi.org/10.1016/j.radonc.2021.03.018.
[20] Ennis RD, Quinn SA, Trichter F, Ryemon S, Jain A, Saigal K, et al. Phase I/II prospective trial of cancer-specific imaging using ultrasound spectrum analysis tissue-type imaging to guide dose-painting prostate brachytherapy. Brachytherapy 2015;14:801–8. https://doi.org/10.1016/j.brachy.2015.06.011.
[21] Henry A, Pieters BR, Siebert FA, Hoskin P. GEC-ESTRO ACROP prostate brachytherapy guidelines. Radiother Oncol 2022;167:244–51. https://doi.org/10.1016/j.radonc.2021.12.047.
[22] Zhao Y, Haworth A, Rowshanfarzad P, Ebert MA. Focal boost in prostate cancer radiotherapy: a review of planning studies and clinical trials. Cancers 2023;15:4888. https://doi.org/10.3390/cancers15194888.
[23] Zamboglou C, Spohn SK, Ruf J, Benndorf M, Gainey M, Kamps M, et al. PSMA-PET- and MRI-based focal dose escalated radiation therapy of primary prostate cancer: planned safety analysis of a nonrandomized 2-armed phase 2 trial (ARO2020-01). Int J Radiat Oncol 2022;113:1025–35. https://doi.org/10.1016/j.ijrobp.2022.04.020.
[24] Schlenter M, Berneking V, Krenkel B, Mottaghy FM, Thomas-Alexander V, Eble MJ, et al. Intensity-modulated radiotherapy of prostate cancer with simultaneous integrated boost after molecular imaging with 18F-choline-PET/CT. Strahlenther Onkol 2018;194:638–45. https://doi.org/10.1007/s00066-018-1282-6.
[25] Eade T, Kneebone A, Hruby G, Booth J, Hsiao E, Le A, et al. Early outcomes and decision regret using PSMA/MRI-guided focal boost for prostate cancer SBRT. Pract Radiat Oncol 2022;12:e201–6. https://doi.org/10.1016/j.prro.2021.09.008.
[26] Vozzo M, Poder J, Yuen J, Bucci J, Haworth A. Use of deformable image registration techniques to estimate dose to organs at risk following prostate external beam radiation therapy and high-dose-rate brachytherapy. J Contemp Brachyther 2021;13:72–9. https://doi.org/10.5114/jcb.2021.103589.
[27] Barber J, Yuen J, Jameson M, Schmidt L, Sykes J, Gray A, et al. Deforming to best practice: key considerations for deformable image registration in radiotherapy. J Med Radiat Sci 2020;67:318–32. https://doi.org/10.1002/jmrs.417.
[28] Poder J, Radvan S, Howie A, Kasraei F, Parker A, Bucci J, et al. Viability of focal dose escalation to prostate cancer intraprostatic lesions using HDR prostate brachytherapy. Brachytherapy 2023;22:800–7. https://doi.org/10.1016/j.brachy.2023.09.001.
[29] Brock KK, Mutic S, McNutt TR, Li H, Kessler ML. Use of image registration and fusion algorithms and techniques in radiotherapy: report of the AAPM radiation therapy committee task group No. 132. Med Phys 2017;44:e43–76. https://doi.org/10.1002/mp.12256.
[30] Mason J, Al-Qaisieh B, Bownes P, Wilson D, Buckley DL, Thwaites D, et al. Multi-parametric MRI-guided focal tumor boost using HDR prostate brachytherapy: a feasibility study. Brachytherapy 2014;13:137–45. https://doi.org/10.1016/j.brachy.2013.10.011.
[31] Mason J, Bownes P, Carey B, Henry A. Comparison of focal boost high dose rate prostate brachytherapy optimisation methods. Radiother Oncol 2015;117:521–4. https://doi.org/10.1016/j.radonc.2015.09.021.
[32] Draulans C, van der Heide UA, Haustermans K, Pos FJ, van Zy JvdV, De Boer H, et al. Primary endpoint analysis of the multicentre phase II hypo-FLAME trial for intermediate and high risk prostate cancer. Radiother Oncol 2020;147:92–8. https://doi.org/10.1016/j.radonc.2020.03.015.
[33] Hearn N, Blazak J, Vivian P, Vignarajah D, Cahill K, Atwell D, et al. Prostate cancer GTV delineation with biparametric MRI and 68Ga-PSMA-PET: comparison of expert contours and semi-automated methods. Brit J Radiol 2021;94:20201174. https://doi.org/10.1259/bjr.20201174.
[34] Zamboglou C, Drendel V, Jilg CA, Rischke HC, Beck TI, Schultze-Seemann W, et al. Comparison of 68Ga-HBED-CC PSMA-PET/CT and multiparametric MRI for gross tumour volume detection in patients with primary prostate cancer based on slice by slice comparison with histopathology. Theranostics 2017;7:228. https://doi.org/10.7150/thno.16638.
[35] Mendez LC, Ravi A, Chung H, Tseng C-L, Wronski M, Paudel M, et al. Pattern of relapse and dose received by the recurrent intraprostatic nodule in low-to intermediate-risk prostate cancer treated with single fraction 19 Gy high-dose-rate brachytherapy. Brachytherapy 2018;17:291–7. https://doi.org/10.1016/j.brachy.2017.10.001.
[36] Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai H, McKenzie M, 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 2017;98:275–85. https://doi.org/10.1016/j.ijrobp.2016.11.026.
[37] Rodda S, Tyldesley S, Morris WJ, Keyes M, Halperin R, Pai H, 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 2017;98:286–95. https://doi.org/10.1016/j.ijrobp.2017.01.008.
[38] Her EJ, Haworth A, Rowshanfarzad P, Ebert MA. Progress towards patient-specific, spatially-continuous radiobiological dose prescription and planning in prostate cancer IMRT: an overview. Cancers 2020;12:854. https://doi.org/10.3390/cancers12040854.
[39] Zhao Y, Haworth A, Reynolds HM, Her EJ, Sun Y, Finnegan R, et al. Patient-specific voxel-level dose prescription for prostate cancer radiotherapy considering tumor cell density and grade distribution. Med Phys 2023;50:3746–61. https://doi.org/10.1002/mp.16264.
[40] Sun Y, Reynolds HM, Parameswaran B, Wraith D, Finnegan ME, Williams S, et al. Multiparametric MRI and radiomics in prostate cancer: a review. Australas Phys Eng Sci Med 2019;42:3–25. https://doi.org/10.1007/s13246-019-00730-z.
[41] Finnegan RN, Reynolds HM, Ebert MA, Sun Y, Holloway L, Sykes JR, et al. A statistical, voxelised model of prostate cancer for biologically optimised radiotherapy. Phys Im Radiat Oncol 2022;21:136–45. https://doi.org/10.1016/j.phro.2022.02.011.
[42] Chan TH, Haworth A, Wang A, Osanlouy M, Williams S, Mitchell C, et al. Detecting localised prostate cancer using radiomic features in PSMA PET and multiparametric MRI for biologically targeted radiation therapy. EJNMMI Res 2023;13:34. https://doi.org/10.1186/s13550-023-00984-5.
[43] Her EJ, Haworth A, Sun Y, Williams S, Reynolds HM, Kennedy A, et al. Biologically targeted radiation therapy: incorporating patient-specific hypoxia data derived from quantitative magnetic resonance imaging. Cancers 2021;13:4897. https://doi.org/10.3390/cancers13194897.
[44] Carlone M, Rink A, Beiki-Ardakani A, Simeonov A, Lao B, Bayley A, et al. MR-guided high-dose-rate (HDR) brachytherapy: simultaneous integrated focal boost to intra-prostatic GTV (s). Brachytherapy 2016;15:S51–2. https://doi.org/10.1016/j.brachy.2016.04.065.
[45] Clark A, Wright G, Mason J, Hulson O, Henry A, Rodda S, et al. Single-and dual-source-strength focal boost planning in low-dose-rate prostate brachytherapy: feasibility study. J Radiot Prac 2023;22:e106.
[46] Luminais C, Nourzadeh H, Aliotta E, Ward K, Cousins D, Showalter T, et al. Dose differentiated high-dose-rate prostate brachytherapy: a feasibility assessment of MRI-guided dose escalation to dominant intra-prostatic lesions. J Contemp Brachyther 2022;14(1). https://doi.org/10.5114/jcb.2022.120035.
[47] Tissaverasinghe S, Crook J, Bachand F, Batchelar D, Hilts M, Araujo C, et al. Dose to the dominant intraprostatic lesion using HDR vs. LDR monotherapy: a Phase II randomized trial. Brachytherapy 2019;18(3):299–305. https://doi.org/10.1016/j.brachy.2019.01.006.
[48] Pouliot J, Kim Y, Lessard E, Hsu I-C, Vigneron DB, Kurhanewicz J. Inverse planning for HDR prostate brachytherapy used to boost dominant intraprostatic lesions defined by magnetic resonance spectroscopy imaging. Int J Radiat Oncol 2004;59(4):1196–207. https://doi.org/10.1016/j.ijrobp.2004.02.055.