Evaluation of focal low dose rate brachytherapy in men with low-intermediate risk prostate cancer

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Abstract

Prostate cancer is the most common cancer diagnosed and the second most common cause of male cancer deaths in Australia. The majority of prostate cancer is localised at diagnosis and amenable to whole gland treatment with curative intent, which is associated with significant morbidity, typically impairment to urinary, bowel or erectile function. To avoid or delay this morbidity, men with low to intermediate risk prostate cancer may be placed on an active surveillance protocol. Through the use of routine monitoring, active surveillance can reserve definitive treatment until local disease progression has been identified, which may not be necessary at all. Focal therapy of the prostate is a hybrid approach which involves ablative treatment of the involved prostate cancer tumour and continued active surveillance of the unaffected gland. Low-dose-rate brachytherapy is an emerging lesion-targeted focal technique that has shown promising oncological and functional outcomes for patients with low-intermediate risk features. It requires more investigation prior to widespread clinical implementation as a focal therapy ablation option.

The aim of this thesis is to explore the 'feasibility' and 'viability' of lesion-targeted focal low-dose-rate brachytherapy as the primary treatment for low-to-intermediate risk prostate cancer. Feasibility encompasses technical and procedural variables and viability pertains to oncological, functional and salvage outcomes. This project is designed with three components.

Project 1 is a retrospective cohort study of twenty-six men with unifocal, low to intermediate grade prostate cancer diagnosed on a combination of multiparametric magnetic resonance imaging and targeted plus template transperineal biopsy, who received focal low-dose-rate brachytherapy at a single institution. This demonstrated focal low-dose-rate brachytherapy is associated with a favourable toxicity profile and a high rate of control of significant prostate cancer at 12-18 months post-treatment. It also provided the foundation for the 'LIBERATE' prospective registry 'Project 3'.

Project 2 is a case study that validates the feasibility of salvage radical prostatectomy necessitated by biochemical and histological failure following focal low-dose-rate brachytherapy. This proof-of-concept report provides an informative template for clinicians who encounter this clinical situation and demonstrated that salvage treatment is not impaired by primary focal low-dose-rate brachytherapy in this case.

Project 3 is a preliminary analysis of the prospective, single-institution but multi-centre clinical registry 'LIBERATE'. Using refined eligibility criteria based on the outcomes of Project 1, 29 men have prospectively undergone targeted focal low-dose-rate brachytherapy. Focusing on the secondary outcome measures of this trial, toxicity evaluation and patient-reported quality of life data have outlined the real-world impact of this treatment modality - namely, that a majority of men will experience acute urinary symptoms that self-resolve, rectal toxicity is minimal at all time points and that some men will experience mild to moderate sexual dysfunction.

This thesis, in conjunction with the completion of the LIBERATE trial, seeks to validate the feasibility and viability of focal low dose rate brachytherapy for low-to-intermediate prostate cancer and provide the cornerstone for future comparative assessment studies.

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Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes one original paper published in peer reviewed journals and one currently unpublished publication with the intention for submission. The core theme of the thesis is focal brachytherapy. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Faculty of Medicine, Nursing and Health Sciences (Alfred Hospital) under the supervision of A/Prof Jeremy Grummet and Dr Andrew See.

(The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.)

Thesis Chapter	Publication Title	Status *(published, in press, accepted or returned for revision, submitted)*	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
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Date: 17/12/2021

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

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Main Supervisor signature: **Date:** 26/12/2021

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"You can't hit a target you cannot see and you cannot see a target you do not have."

Zig Ziglar

1. Introduction

Prostate cancer is the most common cancer diagnosed in Australian men, making up 1/4 of all new male cancer cases in 2019. Prostate cancer is the second most common cause of cancer death in Australian men causing 3264 deaths in 2020 [10]. The majority of prostate cancer is organ-confined at diagnosis [11] and suitable for conventional management treating the entire gland, either with radical prostatectomy (RP) or radiation therapy. These whole gland treatment options are associated with substantial morbidity, typically manifesting as impairment to urinary, bowel and erectile function [12-14]. To avoid or delay this morbidity, men with low to intermediate risk prostate cancer (see below) may be placed on an active surveillance (AS) protocol. Through the use of routine monitoring, AS can reserve definitive treatment until local disease progression has been identified, which may not be necessary at all. The obvious drawback of active surveillance is the potential for the opportunity to cure prostate cancer to be missed. In addition, men have described significant psychosocial stress associated with living with untreated cancer [15,16].

Focal therapy of the prostate is a hybrid approach which involves ablative treatment of the involved prostate cancer tumour and continued active surveillance of the unaffected gland [11]. This approach takes advantage of recent advances in cancer imaging, image-guided biopsies and precision treatment delivery [17-19]. Although prostate cancer is often multifocal, it is the index lesion that is typically responsible for biochemical or metastatic progression with most metastatic disease arising from a single precursor cancer cell [20,21]. In addition, a significant minority of prostate cancers are truly unifocal. As such, treating only the diseased part of the prostate should be as effective as whole gland therapy with the potential for less treatment related toxicity [22,23]. Focal therapy may prevent, or in some cases delay, the need for future radical therapy and associated toxicity.

A variety of treatment modalities, including radiotherapy, are currently in use for focal therapy to the prostate in an investigational context. Whole gland radiotherapy delivered as either low dose rate (LDR) or high dose rate (HDR) brachytherapy has substantial, long-term data for successfully treating low and intermediate risk prostate cancer. As a monotherapy, low dose rate brachytherapy achieves good oncological results [24] and is well-recognised as a standard treatment option in this setting [25]. Sylvester et al reported a 15-year biochemical relapse-free survival of 85.9% for low and 79.9% for intermediate risk disease [26]. From a review of seven single-arm studies of focal brachytherapy (n = 541 patients, follow up range of 2-5 years), local disease progression or recurrence was in the range of 0% to 17% and the rate of urinary incontinence less than 5% across all studies [27]. However, despite the global increase in the use of focal therapy modalities to treat low and intermediate risk prostate cancer, robust evidence to support its efficacy and optimal utilisation is still maturing [11,27].

1.1 Prostate Cancer

1.1.1 Anatomy and Physiology

1.1.1.1 Gross Anatomy

The prostate is an accessory gland only found in the male reproductive system. On average the gland weighs 20-25 grams and is about the size of a walnut [28]. It is located above the urogenital diaphragm and below the bladder, surrounding the proximal urethra. The prostate has a four-sided pyramidal shape with an apex distally and base proximally as well as anterior, posterior and inferolateral surfaces. The *base* directly adjoins the inferior surface of the bladder allowing for the urethra to enter the prostate and travel towards the gland's apex. The *apex* is in contact with the superior fascia of the urogenital diaphragm and forms the prostates most inferior point. *Anteriorly* the prostate sits behind the pubic arch and is fixed by the puboprostatic ligaments to the pubic bones. *Inferolateral* the prostate is supported by the pelvic floor and is held by the pubourethralis component of levator ani. *Posteriorly,* Denovillier's fascia separates the prostate capsule from the lower rectum [29].

Penile erections are orchestrated by the complex interplay of neuronal and vascular components. Importantly the pelvic plexus, responsible for delivering the neurotransmitters that are crucial for penile erection, course along the inferolateral aspect of the prostate capsule close to the tips of the seminal. These neurons are accompanied by vasculature and form neurovascular bundles first described by Walsh et al [30]. Erectile dysfunction (ED) results when these nerves are severed, for example following a non-nerve sparing radical prostatectomy (RP). ED can also commonly occur even when the erectile nerves are spared during RP, due to traction injury [31].

The male urethral sphincter complex is controlled by five main structures, these elements are responsible for urinary continence. Combining both skeletal and smooth muscle components, they include: the internal sphincter, the ureterotrigonal muscles, the levator muscles, the rhabdosphincter and the detrusor muscle [32]. The smooth muscle component forms the internal and external sphincter and is derived from the musculature of the urethra. These sphincters can be identified by their distinct layer of longitudinal smooth muscle surrounded by circular smooth muscle which results in narrowing of the urethra when contracted, providing continence [33]. The skeletal muscle sphincter (rhabdosphincter), surrounds a large portion of the membranous urethra resulting in higher urethral resistance which produces an active continence [33].

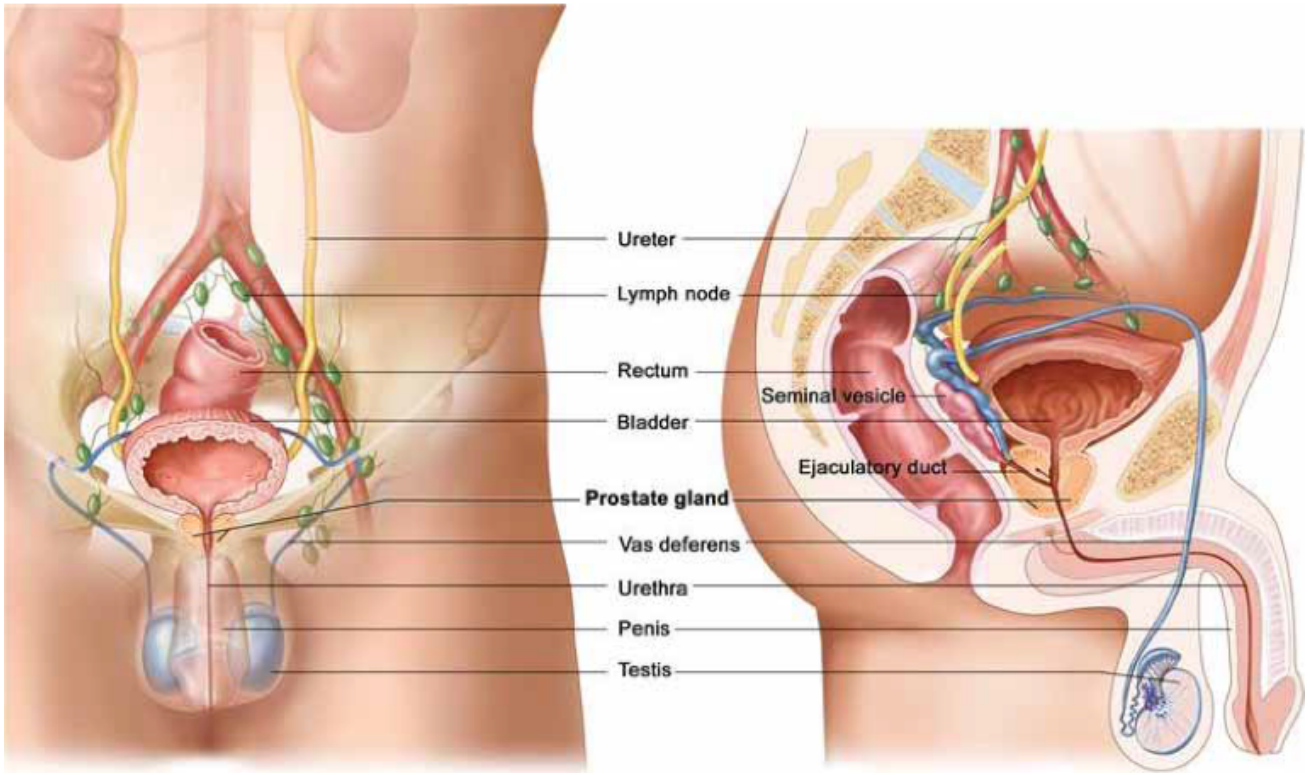

Figure 1: Anatomy of the prostate gland
Male reproductive and urinary tract anatomy. Taken from *Prostate Cancer in NSW*, Alam et al, 2009 [3].

1.1.1.2 Zonal Anatomy

Anatomically, the prostate is separated into three distinct zones. Surrounding the ejaculatory ducts is the wedge-shaped *central zone*, which forms the base of the prostate and accounts for 25% of prostate volume. The *transitional zone* lies proximal to the central zone apex and surrounds the distal pre-prostatic urethra, contributing 5% to the total volume of the prostate. The clinically important *peripheral zone*, is shaped like a cup and encompasses the central zone posteriorly and inferiorly forming the majority of prostate volume (70%) in young men. Importantly, most prostate cancer arises from the peripheral zone [29].

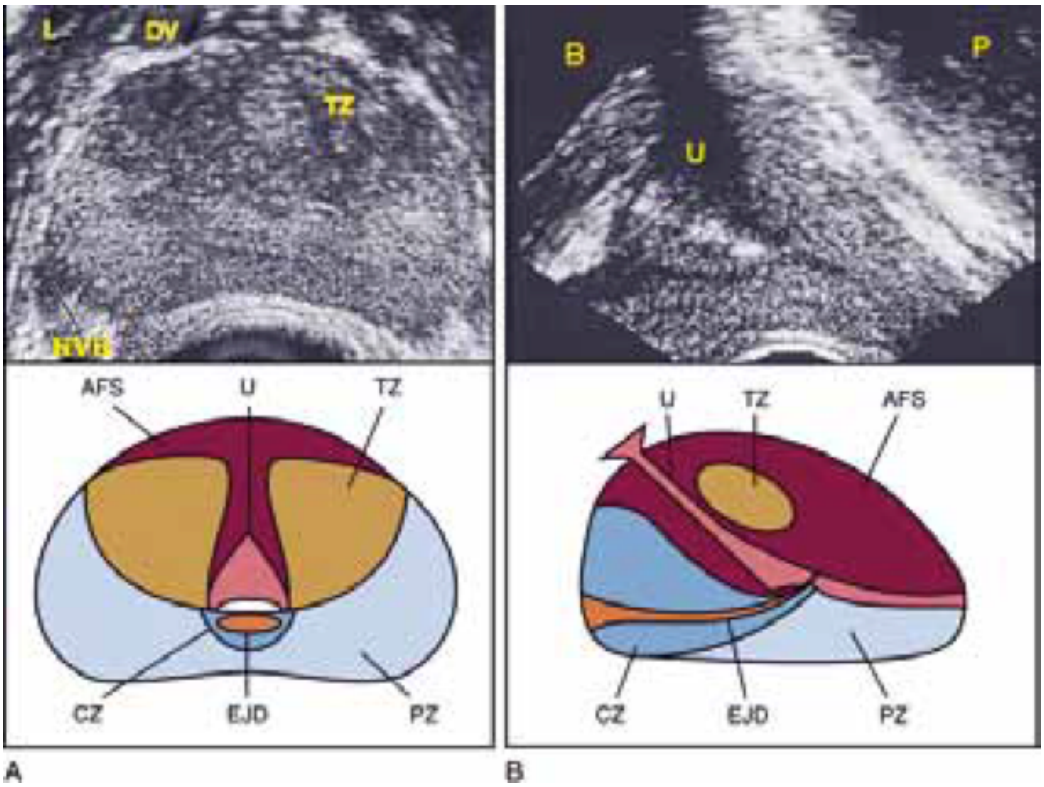

Figure 2: Zonal anatomy of the prostate gland
Ultrasound images of a normal prostate (above), with diagrams (below) demonstrating zonal anatomy. A, Transverse view. B, Sagittal view. AFS, anterior fibromuscular stroma; CZ, central zone; DV, dorsal vascular complex; EJD, ejaculatory ducts; NVB, neurovascular bundle; L, levator muscles; PZ, peripheral zone; TZ, transition zone; U, urethra. Taken from *Campbell-Walsh Urology* [6].

1.1.1.3 Physiology

The prostate gland has an exocrine function, secreting an alkaline fluid that combines with male ejaculate and increases sperm mobility. Mechanistically, the acidity found in vaginal secretions that would otherwise impair sperm motility is counteracted by the alkaline nature of prostatic fluid [6]. This in turn improves the chances of a successful fertilization of the ovum. Additionally, it is thought that prostate-specific antigen (PSA), a prostate derived protein that is abundant in seminal fluid also contributes to sperm mobility [34].

1.1.2 Epidemiology

1.1.2.1 International

Globally, prostate cancer is the second most commonly diagnosed cancer in men and causes the fifth most cancer deaths [35]. The incidence rate varies by region, with the highest age-standardized rate (ASR) in Oceania (79 per 100,000) and North America (73 per 100,00) and the lowest ASR in Africa (26 per 100,00) and Asia (11 per 100,00) [36]. Internationally, 375,304 men were reported to have died from prostate cancer in 2020, increasing from 256,000 deaths in 1990 [5,37]. The wide disparity seen in global incidence rates of prostate cancer (Figure 4) can

be in part explained by substantial worldwide variation in the use of PSA screening programs that detect prostate cancer in asymptomatic individuals [38].

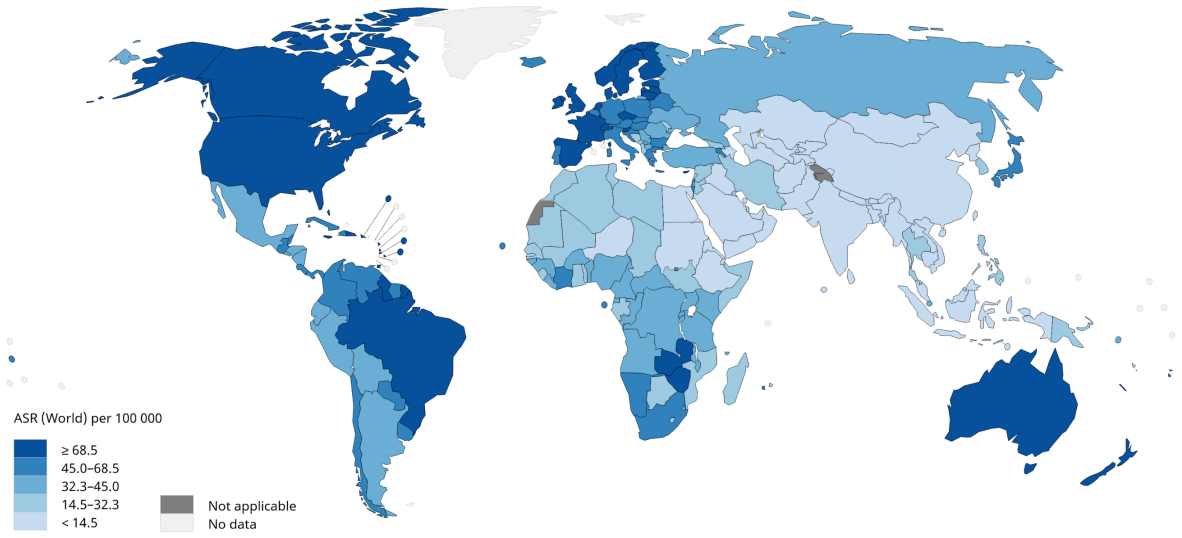

Figure 3: Estimated prostate cancer ASR incidence rates worldwide in 2020 in males
Data obtained from Globocan 2020 [5].

1.1.2.2 Australia

In Australia, 3264 men died of prostate cancer in 2020 making it the second most common cause of cancer death in males. Using data from 2019, new prostate cancer diagnoses in Australia counted for 24% of all new cancer diagnosis in males [10]. Although no racial difference in prostate cancer mortality within Australia has been identified, Aboriginal and Torres Strait Islander men are less commonly diagnosed with prostate cancer. This may be due to differences in: the frequency of testing, population age stratification and differing risk profiles[10].

1.1.3 Natural History

The complete natural history of prostate cancer is still being determined. The current hypothesis is that prostate cancer may stem from injured prostate epithelium, gradually developing over time [39]. Further complicating matter is prostate cancer's propensity to be multifocal and heterogeneous which increases the variations and makes patterns harder to identify [40]. Based on autopsy studies, around 1/3 of all men over the age of 50 years will have some histological evidence of prostate cancer. This proportion increases markedly with age. Although clinically insignificant in most cases, this finding highlights the variability and protracted nature of prostate cancer [41,42].

It can be difficult to distinguish between proliferative and indolent prostate disease. A prostate biopsy might detect cancer that is diagnosed as localised then histologic analysis following

prostatectomy may reveal cancer growth beyond the borders of the prostate gland or even metastatic disease. Conversely, a man diagnosed with prostate cancer may not suffer any significant morbidity or mortality. It is therefore essential to determine the likelihood that a certain lesion will progress beyond localised disease [43]. Importantly, prostate cancer progression has been linked to tumour grade. High-grade tumours are more aggressive and more poorly differentiated than low-grade. Therefore, collecting tissue samples of the prostate in an accurate and timely manner is important so that appropriate therapeutic intervention is not delayed [44,45].

Prostate cancer symptoms can be mild and varied delaying early clinical diagnosis. Some men complain of dysuria, haematuria, urinary frequency, urinary urgency or nocturia. However localised prostate cancer is typically asymptomatic and commonly identified by screening [46]. Advanced prostate cancer can present with symptoms caused by metastatic cancer spread, such as bone pain from vertebral metastasis [47].

1.1.4 Risk Factors and Prevention

The most important risk factors for prostate cancer include age, genetic factors and ethnicity.

Out of all human malignancies, prostate cancer has one of the closest associations with age. Prostate cancer hardly ever occurs in men younger than 40 and its peak incidence is in men aged between 65 and 74 (Figure 5)[48]. As illustrated by a review of autopsy studies undertaken by Delongchamps et al, the widespread prevalence of prostate cancer dramatically increases with age: 20 to 30 years (2-8%), 31 to 40 years (9-31%), 41 to 50 years (3-43%), 51 to 60 years (5-46%), 61 to 70 years (14-70%), 71 to 80 years (31-83%), 81 to 90 years (40-73%)[49]. The variability expressed in the percentage range is likely a reflection of differences in geographical, ethnic, environmental or diagnosis/management regimens.

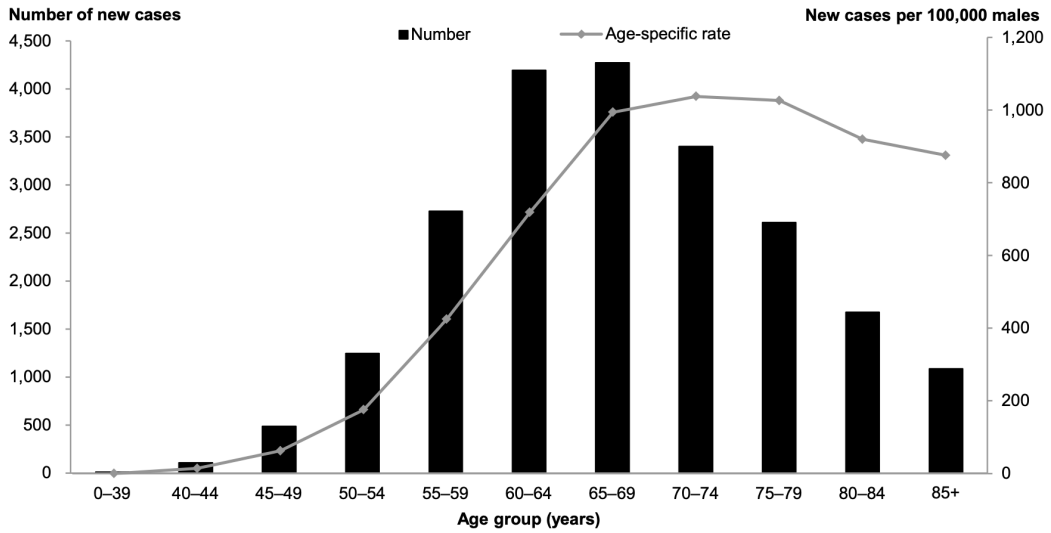

Figure 4: Incidence rates of prostate cancer (number and age-specific rate) among males, by age group, Australia, 2009

Source: AIHW Australian Cancer Database 2009; Table S3.1. [4]

Family history and genetic factors are strongly linked to prostate cancer. The lifetime risk of a man developing prostate cancer is doubled if they have one first-degree relative with prostate cancer, while having two affected relatives increases the risk by 3.5-fold [50]. In addition, men who have a positive family history for other cancers with an inherited component may also be at an increased risk. Specifically, men who have a positive family history for breast cancer also have a greater likelihood of developing prostate cancer [51]. As demonstrated by Momozawa et al, who compared 7636 men with prostate cancer to 12,366 cancer free controls and found that prostate cancer risk is significantly associated with BRCA2 variants that are proven to increase breast cancer risk [52].

Prostate cancer rates vary considerably by race. In the United States of America (USA), the highest incidence rate was observed in Black men (175 per 100,000 persons), followed by White men (105 per 100,000), then Asian/Pacific Islander (56 per 100,000) and lastly American Indian/Alaska Native (54 per 100,00) [48].The explanation for these differences is likely multifactorial and related to variability in screening and treatment access, socioeconomic conditions and underlying genetic factors that link to more biologically aggressive disease [35].

In regards to the prevention of prostate cancer, men with 5-alpha reductase (5-AR) deficiency, who lack the enzyme that modifies testosterone to the more potent dihydrotestosterone (DHT), do not develop prostate cancer [53]. By targeting this hormonal dependency, 5-AR inhibitors (finasteride, dutasteride) may pharmacodynamically disrupt prostate carcinogenesis. When investigated, it was shown that men who receive 5-AR inhibitors do have a reduced risk of low-grade (Gleason score ≤6) prostate cancer but this does not translate to a survival benefit. Further, these studies also showed that men taking 5-AR inhibitors are at a greater risk of

developing high grade prostate cancer[54,55]. Upon further analysis, this finding is unlikely to indicate a true modification to the biology of prostate disease. Rather it likely results from detection bias as 5-AR inhibitors shrink the prostate and therefore make higher grade lesions easier to identify [56,57]. When considered in conjunction with the known treatment-related side effects (decreased libido, erectile dysfunction, gynecomastia) 5-AR inhibitors are not recommended for chemopreventive therapy [58].

Lastly, certain foods and vitamins have been theorized to influence a man's risk of developing prostate cancer. Evidence supporting nutrition for chemoprevention is increasing, with some dietary elements (ie selenium [59], vitamin E, cruciferous vegetables [60], carotenoids [61] and fish/marine omega 3 fatty acids [62]) believed to be preventative. Conversely some foods (ie grilled meats, saturated fat [63], zinc at high doses [64] and heterocyclic amines) may predispose towards prostate cancer. To date, no randomized, prospective studies have identified any significant results and further clinical trial data are needed before nutritional supplementation can be considered standard of care. Dietary advice consistent with the established literature for preventing heart disease is likely to provide benefit without harm to patients [65,66].

1.1.5 Diagnosis

Prostate cancer is typically identified by either an abnormal prostate-specific antigen (PSA) value or anomalous digital rectal exam (DRE). Positive results from either test are not diagnostic and usually instigate further investigation. When both tests are interpreted together improved cancer detection rates have been demonstrated [67].

1.1.5.1 Digital Rectal Examination

The DRE is a medical examination that aims to manually interrogate the prostate for abnormalities such as asymmetry, hardness or suspicious nodules [68]. Although DRE has a high specificity when utilised by urologists for the detection of prostate cancer (94%), it is not very sensitive (59%) and has a low positive predictive value (28%)[69]. In the primary care setting, the sensitivity and specificity of DRE is lower at 51% and 59% respectively [70]. In addition, DRE may act as a deterrent for men to undergo prostate cancer screening due to physical discomfort [71]. Anatomically DRE is limited to only assessing the lateral and posterior part of the gland for tumours and also by definition cannot detect stage T1 cancer [72]. As such, DRE is no longer recommended in the primary care setting but is still conducted by urologists and is included in expert guidelines [73-75].

1.1.5.2 Prostate Specific Antigen

PSA is a glycoprotein enzyme that is uniquely secreted by prostate ductal epithelial cells and neoplastic prostate tissue which can be measured via a simple blood test. An elevated PSA

result is non-specific but is consistently expressed in most prostate cancer. However, an abnormal PSA result does not diagnose prostate cancer and may also identify other prostate pathology such as inflammation, perineal trauma or prostate enlargement [6]. PSA testing is multi-purpose providing an estimate of prostate cancer risk, a calculation of tumour stage and aggressiveness as well as gauging the effectiveness and utility of treatment [76]. Standardized PSA reference ranges exist for different age groups in order to account for the natural phenomenon of prostate gland enlargement with increasing age [77](Table 1). Although the exact PSA cut-off to delineate abnormality is controversial, historically a concentration greater than 4.0 ng/ml is treated as pathological. At this value, PSA testing has a high specificity (91%) but low sensitivity (21%) and low positive predictive value (32%) for the detection of prostate cancer. When the PSA cut off is reduced to 3.0 ng/ml, the specificity of testing decreases (85%) but its sensitivity increases (32%) [73]. As such, specificity and sensitivity are inversely proportional, with lower PSA limits linked to increased false positive results [78]. Advances in PSA testing have helped refine the interpretation of an elevated concentration and include: PSA density, velocity and serum free and bound PSA ratio [79].

Age Range	PSA (ng/mL) 50th percentile (median)	PSA (ng/mL) 95th percentile (upper limit of normal)
40-49	0.65	2.0
50-59	0.85	3.0
60-69	1.39	4.0
70-79	1.64	5.5

Table 1: Age-based normal ranges for PSA (ng/mL)

Adapted from: Oesterling JE, Jacobsen SJ, Klee GG, Pettersson K, Piironen T, Abrahamsson PA, Stenman UH, Dowell B, Lövgren T, Lilja H. Free, complexed and total serum prostate specific antigen: the establishment of appropriate reference ranges for their concentrations and ratios. J Urol. 1995 Sep;154(3):1090-5. doi: 10.1016/s0022-5347(01)66984-2. PMID: 7543605 [9].

1.1.5.2.1 PSA Density

By dividing PSA value into prostate volume, PSA density helps to delineate between benign and malignant disease, with lower values suggestive of benign prostate hyperplasia (BPH) [80]. Difficulties with prostate volume measurement are inherent to this calculation, with error and variation contributing up to a 15% difference in a patient's PSA density with repeated measurements [81].

1.1.5.2.2 PSA Velocity

PSA velocity measures the rate of change in serum PSA. Prostate cancer is more likely to cause a rapid rise in PSA levels than benign conditions [82]. Carter et al, found in that men whose PSA level increased by more than 0.35ng/ml per year had a greater prostate cancer specific mortality at 15 years than men whose PSA rose more slowly [83]. From a clinical perspective, the utility of PSA velocity is reduced by intra-patient variability in serum PSA. To counter this, measurements taken over a greater time period can improve the diagnostic useability of PSA

velocity testing, with at least three consecutive values usually required to distinguish biological from pathological PSA variation [84].

1.1.5.2.3 Serum Free and Bound PSA

Prostate cancer cells secrete less PSA than normal tissue but due to abnormal cancer cell architecture more PSA leaks into the bloodstream avoiding the normal proteolytic process that produces unbound 'free' PSA. As a result, prostate cancer causes men to have lower serum levels of free PSA in comparison to men with a normal prostate or BPH [85]. As demonstrated by Catalona el al, the free/total PSA ratio (f/t PSA) can increase test specificity when the total PSA is suggestive but not conclusive. They found that men with a PSA value between 4-10 ng/ml and f/t PSA < 10% had a much greater probability (56%) of prostate cancer compared to men with the same PSA value and a f/t PSA > 25% (8%) [86].

1.1.5.3 Novel Biomarkers

In addition to PSA, a number of blood- and urine- based molecular and genetic tests have been developed in order to help identify prostate cancer as early as possible. Amongst these novel biomarkers that are commercially available, perhaps the most notable are Prostate Cancer Antigen 3 (PCA3) and the Prostate Health Index (PHI).

PCA3 is a urine based prostate cancer biomarker that detects a prostate specific non-coding RNA gene that is overexpressed in the setting of prostate cancer [87]. When compared to serum PSA testing, PCA3 is more specific with higher positive and negative predictive values but it is a less sensitive test [88,89]. Of note, PCA3 levels are unrelated to prostate volume, whereas PSA values are dependent [90]. In the clinical context, PCA3 can be used to help determine the likelihood of prostate cancer in the cohort of men undergoing repeat prostate biopsies [91,92]. In addition, there is some evidence that PCA3 correlates with tumour volume and predicts extracapsular extension [93,94].

The PHI is a mathematical equation that calculates a patient's risk of prostate cancer based upon PSA, free PSA and a precursor from of PSA (p2PSA). p2PSA is the most stable isoform of PSA and has shown to correlate with increasing specificity for prostate cancer [95]. The PHI formula is defined as: (p2PSA/free PSA) $\times \sqrt{PSA}$. PHI is based on the premise that men with a higher level of p2PSA and PSA but a lower level of free PSA are at a greater risk of clinically significant prostate cancer[96]. Lazzerie et al demonstrated in the large multicentred European trial PRO-PSA, that using PHI in men with a PSA of 2-10ng/ml or suspicious DRE was more accurate than PSA or f/t PSA testing at predicating an initial positive prostate biopsy [97]. PHI is a cheap and simple blood test that has been shown to improve the detection of aggressive prostate cancer (Gleason score ≥7) [98]. It should be considered to be a viable component of multivariable prostate cancer screening.

Of note, several groups have compared PCA3 to PHI [99-101]. Both biomarkers have shown similar results for the prostate cancer detection. However, PCA3 testing has greater utility in

identifying prostate cancer in men undergoing repeat prostate biopsies and PHI results more accurately correlate with a patient's Gleason score.

1.1.5.4 Prostate Biopsy

Prostate biopsy is a minimally invasive procedure that provides prostate tissue for the histologic diagnosis of prostate cancer. There are two main prostate biopsy approaches, either transrectal or transperineal. Prostate tissue can also be obtained via a transurethral approach and is commonly analysed for cancer following a transurethral resection of prostate (TURP). However, due to the anatomical difficulty in sampling the peripheral zone of the prostate transurethrally, TURP should primarily be reserved for the management of lower urinary tract symptoms.

Transrectal Ultrasound Guided Prostate Biopsy

Transrectal Ultrasound (TRUS) guided prostate biopsy is the traditional technique for acquiring prostate tissue. TRUS biopsy may be undertaken as an office-based procedure or performed in the operating suite and is usually undertaken using local anaesthesia by a trained urologist. The patient is usually placed in the lateral decubitus position with their hips and knees flexed to 90-degrees, under TRUS probe guidance the biopsy needle is then systematically directed to various sections of the prostate (Figure 6)[102]. Because the biopsy needle passes through the rectum, TRUS prostate biopsy has a post-biopsy infection rate of 0.6-2.9%[103]. As such the administration of prophylactic antibiotics is recommended prior to TRUS biopsy, with fluoroquinolone antibiotics the most commonly selected class due to their favourable pharmacodynamic and pharmacokinetic profiles [104].

Transperineal Prostate Biopsy

Transperineal (TP) prostate biospy is an alternative method of prostate biopsy. It typically utilizes a transrectal ultrasound probe and brachytherapy template grid which enables sampling through the perineal skin. As the biopsy trocar remains 'sterile', there is a negligible risk of infectious complications [105]. Theoretically, this means that preoperative prophylactic antibiotics are not needed [106]. In addition, due to the TP angle of biopsy it is better at sampling the apical and anterior prostate regions compared to TRUS biopsy [107,108]. As illustrated by Vyas et al, 17% of patients whose initial TRUS biopsy resulted in a false negative, later had prostate cancer identified in the anterior region on TP biopsy [109].

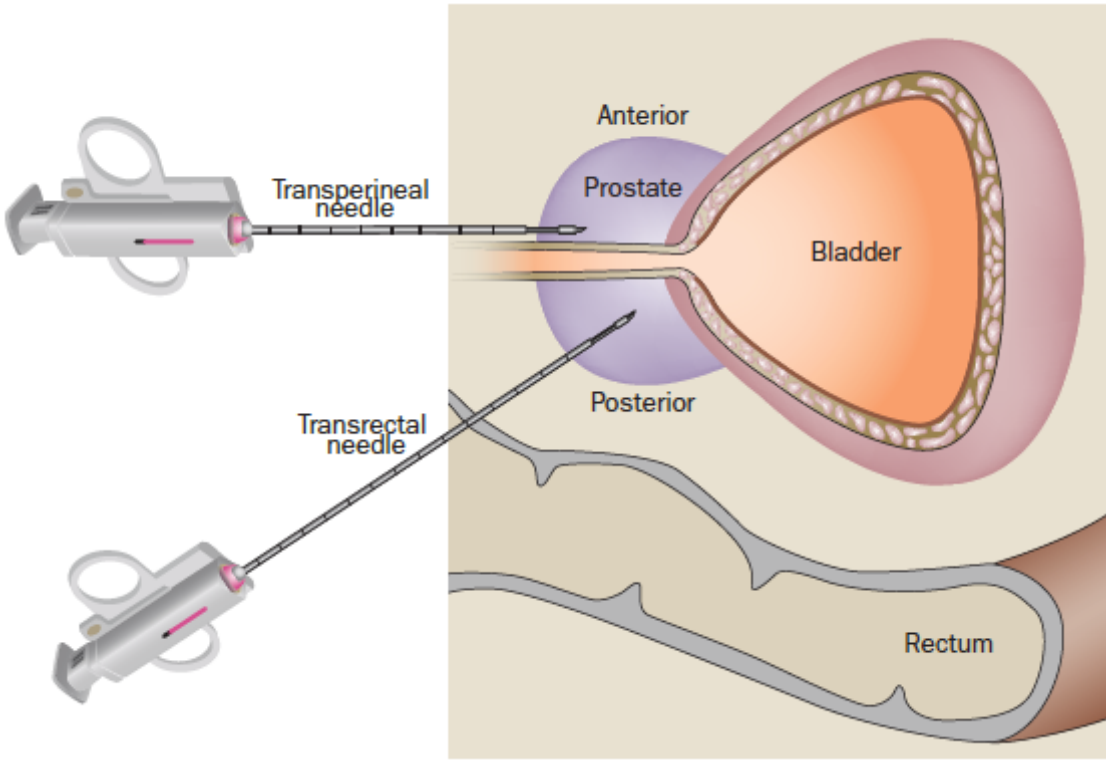

Figure 5: Difference of approach between transperineal and transrectal biopsy
Comparison between in approach between transperineal and transrectal biopsy techniques. Image taken from *Transperineal biopsy of the prostate-is this the future?,* Chang et al, 2013 [7].

1.1.5.5 Prostate Biopsy Interpretation

The overwhelming majority (>95%) of cancer found in the prostate is adenocarcinoma. Although other types of malignancy occurring in the prostate (eg carcinosarcoma, lymphoma, transitional cell carcinoma, stromal sarcoma or basal cell carcinoma) is possible. This thesis will focus on adenocarcinoma.

Histological diagnosis of prostate adenocarcinoma is based on a number of cytologic and architectural characteristics. Cytologically these include: darker hematoxylin and eosin-stained amorphous secretions, enlarged and irregular nucleoli, blue-tinged mucin and hyperchromasia. Architecturally prostate cancer glands are smaller than benign glands and malignant cells commonly grow with an irregular and haphazard infiltrative pattern (Figure 7) [110].

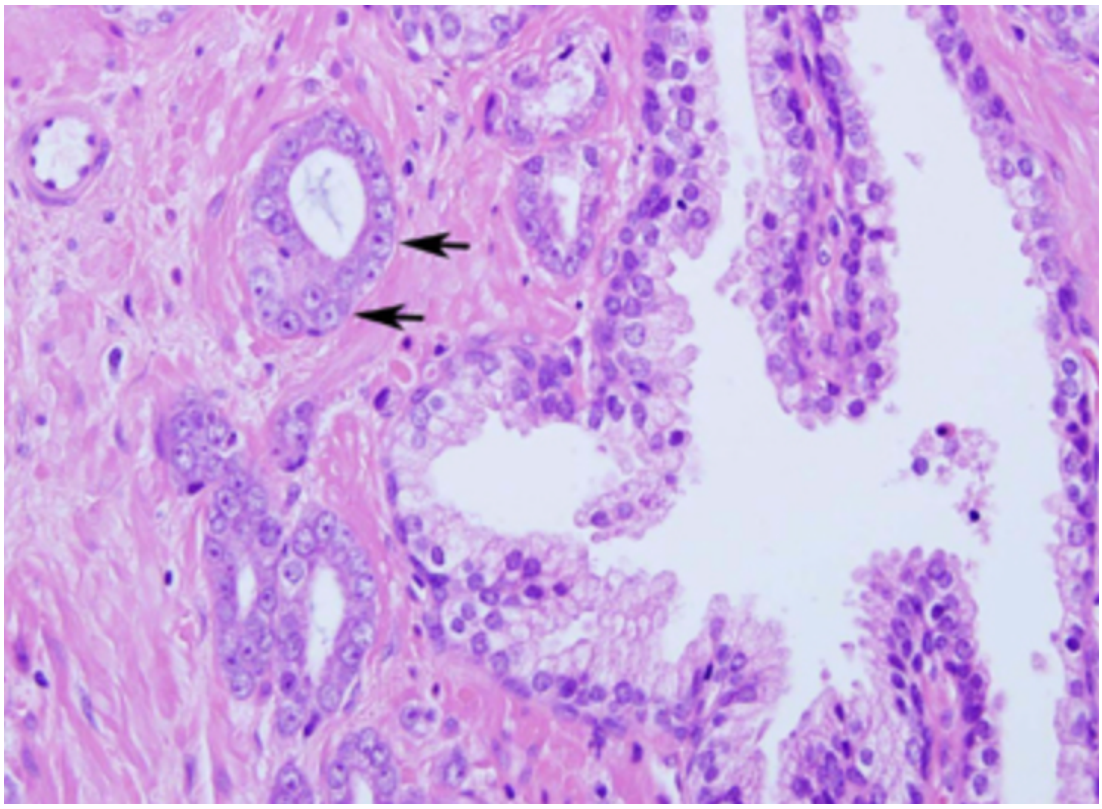

Figure 6: Prostate Cancer demonstrating prominent nucleoli
A high-power photomicrography of hematoxylin-and eosin-stained prostate gland showing prostate adenocarcinoma. Illustrative arrows demonstrating enlarged and irregular nuceoli with amorphous secretions. This can be compared to the large, benign gland taking up the entire right half of the slide. *Courtesy of Ximing Yang, MD, © 2021 UpToDate, Inc. and/or its affiliates. All Rights Reserved.*

1.1.5.5.1 Gleason Grading System

The Gleason score is a grading system that can be used to determine the aggressiveness of prostate cancer. It is determined by microscopic examination of prostate cancer tissue and the assessment of its architectural features. The Gleason score allows for prostate cancer prognostication, with higher scores signifying poorer patient outcomes [111]. Scores ranging from 5 (poorly differentiated tissue) through to 1 (well differentiated tissue), are assigned to the most common and second most prevalent pattern. This gives a theoretical range from 2-10 although in practice scores less than 3 are not given. If the tumour contains a third component of higher-grade disease then that is graded as the secondary pattern [112].

1.1.5.5.2 International Society of Urological Pathology Grading System

In 2014 the International Society of Urological Pathology (ISUP) endorsed an innovative grading system that expands on the Gleason scoring system (Table 2) [2]. The new Grade Group classification does not replace the Gleason score rather it provides a simplified and more accurate risk stratification for patients [113]. Including the ISUP grade group in addition to the Gleason score is current practice in prostate cancer pathology reporting, for example "prostate adenocarcinoma, Gleason score 3+4 (ISUP 2, with 20% Gleason pattern 4 cancer)".

Grade Group	Gleason score and pattern
1	Grade 6 (3+3)
2	Grade 7 (3+4)
3	Grade 7 (4+3)
4	Grade 8 (4+4, 3+5 or 5+5)
5	Grade 9 or 10 (4+5, 5+4 or 5+5)

Table 2: ISUP grade group classification system

Adapted from: Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol 2016; 40:244 [2].

1.1.5.5.3 Perineural Invasion and Extraprostatic Extension

Perineural invasion (PNI) is defined as cancer invasion into surrounding nerves and if present in a prostate biopsy specimen increases the risk of extraprostatic extension following radical prostatectomy [114-116]. PNI on pre-treatment biopsy is also predictive of disease recurrence following primary external beam radiotherapy [117].

If extraprostatic extension is identified by the pathologist then the patient's disease is considered to be locally advanced. Although it is uncommon to identify extraprostatic extension directly from a prostate biopsy sample it is possible as demonstrated by Varma et al who found one case in a series of 150 malignant needle biopsy specimens [110].

1.1.5.6 Insignificant Prostate Cancer

Clinically insignificant prostate cancer is typically thought of as cancer that will not impact the patient over their lifetime. Localised, small volume, low-grade prostate cancer commonly maintains an indolent course that is unlikely to progress to biologically significant disease if left untreated [118,119]. Currently, the definition of insignificant prostate cancer is typically based on three well-established prognostic factors determined from pathological assessment of radical prostatectomy cases [120]:

- Gleason score ≤ 6 without Gleason pattern 4 or 5 – although a small percentage of pattern 4 (<10%) has been accepted by some studies.
- Organ-confined disease – no seminal vesical invasion, extraprostatic extension or lymph node involvement.
- Tumour volume <0.5cm^3

Clinically significant cancer is not solidly defined within the literature, with no one definition universally accepted [121]. A number of publications have suggested that the presence of Gleason pattern 4 (or above) should be deemed clinically significant as active surveillance is typically no longer considered to be an appropriate management option [122-124]. Optimal patient management depends on the diagnostic process continuing to improve to ensure that patients with significant cancer are identified. By better distinguishing between significant and

insignificant disease, morbidity and mortality can be reduced by limiting overtreatment and over-detection of otherwise indolent cancer.

1.1.5.7 Prostate Cancer Index Lesion and Multifocality

[125,126]Importantly, Gundem et al has demonstrated through genomic sequencing and sophisticated statistical modelling that nearly all prostate cancer metastases originate from a single prostate cancer cell in the primary tumour which is termed the 'index lesion' [127]. The index lesion is typically described as the biggest focus of the greatest Gleason score prostate cancer within the prostate [20,128]. Low-grade non-index lesions rarely metastasise and are extremely unlikely to cause death whereas the 'index' lesion can be lethal [21]. This concept has been expanded through the growing understanding of clinically significant versus clinically insignificant prostate cancer. As such, men who only have clinically insignificant disease, derive no certain benefit from active treatment [129].

Prostate cancer is also considered to be multifocal with multiple genetically distinct cancer cell clones [125,126]. Rates of multifocality range between 50% to 90% [130-132] . The impact of this biological feature adds to the complexity of prostate cancer diagnosis and management as independent tumor foci have unique genetic characteristics that change the behaviour of each lesion. Tumor staging and prognosis depends on accurate anatomical and histological interrogation of the gland to properly ensure all lesions are identified and properly delineated by grade and size and the index lesion is correctly identified. As discussed further in section 1.1.2.1, multifocality poses a number of challenges for focal ablative treatments with patient selection and imaging fidelity being paramount.

1.1.5.8 Multiparametric Magnetic Resonance Imaging

1.1.5.8.1 General Principles

Magnetic Resonance Imaging (MRI) is an imaging technology that captures radiofrequency energy released from certain atomic nuclei when they are placed in an external magnetic field. Most commonly hydrogen atoms are used due to their natural abundance in people and biological organisms, particularly fat and water. When inside the magnetic field of the scanner, the protons (positively charged spinning nucleus of hydrogen atoms) align to either parallel or anti-parallel to the direction of the field. As these protons relax, the energy they admit is captured by antennas by a radio antenna called a body coil that surrounds the patient. An image can then be formed based on the variation in signal intensities measured captured from different locations. These signal intensities are represented as relative points of brightness or darkness, based on the strength of the magnetic field and tissue characteristics [133,134].

1.1.5.8.2 Prostate MRI Technique

Prostate cancer detection is enhanced by the addition of prostate MRI. The PRECISION study demonstrated that MRI-guided biopsies identified more clinically significant cancer compared with biopsy alone [17]. Key advancements in MRI technology have contributed to its increased

clinical utility. The adoption of stronger magnets, 1.5 to 3.0 Tesla magnetic field strength, has improved image resolution and shortened the examination time to approximately 40 minutes. In addition, the utilisation of multiparametric MRI (mpMRI) imaging that includes three individual imaging sequences (T2-weighted imaging, diffusion-weighted imaging and dynamic contrast-enhanced imaging) allow for more interrogation and assessment of the prostate. Using these enhanced sequences, mpMRI has a reported sensitivity of 63-96% and specificity of 86-96% [135-137]. The clinical guidelines of both the European Society of Urogenital Radiology (ESUR) and the European Association of Urology (EAU) recommend using T2 weighted, diffusion-weighted and dynamic contrast-enhanced sequences as standard for mpMRI [138,139].

- T2-Weighted Imaging (T2WI) → Outlines zonal anatomy in greater detail improving prostate cancer detection and stage determination [140]. On T2-wighted imaging, tumour in the peripheral zone is easier to identify as it has a low signal intensity compared to normal tissue [141]. However, low signal intensity on T2WI is not specific for cancer and can also result from BPH, infection, inflammation, fibrosis or radiation [135,138,139]. As such, T2WI has a high sensitivity but low specificity [142].
- Diffusion-Weighted Imaging (DWI) → Utilises the variances in cellular density between benign and malignant tissue to identify prostate cancer. Water molecules diffuse through cancerous tissue less freely than normal tissue, resulting in a reduced apparent diffusion coefficient (ADC) value and greater signal intensity [136]. This sharp distinction between normal tissue and malignancy facilitated by DWI boosts the specificity and sensitivity of mpMRI when added to standard T2-weighted imaging [143,144].
- Dynamic Contrast Enhanced (DCE) Imaging→ As a result of malignancy induced angiogenesis and vessel permeability, prostate cancer has greater contrast enhancement compared to normal tissue. DCE allows for detailed information regarding microvessel permeability and tissue perfusion to be obtained via a rapid sequence of T1-weighted images taken immediately prior, during and after the administration of a gadolinium contrast agent [142]. DCE imaging principally helps improve mpMRI specificity by helping to delineate malignancy from benign tissue on T2-weighted images. When T2 weighted imaging is combined with DCE-MRI the reported sensitivity and specificity are 70-96% and 88-97% respectively, compared to T2-weighted imaging alone that has a reported sensitivity of 75-94% and a specificity of 37-53% [142,145]. There is also an added role for DCE-MRI in determining patient prognosis and their response to treatment, as the degree of tumour angiogenesis correlates with pathological staging and tumour aggressiveness [142].

1.1.5.8.3 MRI Interpretation

Reporting standardisation through the implementation of the *Prostate Imaging Reporting And Data System* (PI-RADS), now updated to PI-RADSv2.1, has revolutionised how mpMRI

prostate scans are reported [146]. Designed by the International Prostate MRI Working Group, it is a standardized and objective framework for prostate cancer MRI reporting worldwide. Baseline criteria for PI-RADSv2.1 includes technical standards for scanning hardware and protocols for image collection, which mandates a T2WI, DWI and DCE series in all examinations. Although the existing data on evaluating PI-RADSv2 is highly heterogeneous, a recent meta-analysis demonstrated that it has a high sensitivity, when Gleason score ≥7 is counted as a positive test [147,148].

The PI-RADS system uses a five-point grading system that classifies prostate lesions by their likelihood of being cancerous [146].

- *PI-RADS 1* – Clinically significant cancer is highly unlikely to be present.
- *PI-RADS 2* – Clinically significant cancer is unlikely to be present.
- *PI-RADS 3* – The presence of clinically significant cancer is equivocal.
- *PI-RADS 4* – Clinically significant cancer is likely to be present.
- *PI-RADS 5* – Clinically significant cancer is highly likely to be present.

The main drawback for the PI-RADSv2.1 reporting system, despite providing a consistent MRI interpretation structure, is variation in reporting quality and reproducibility. This may be due to mpMRI analysis being heavily reliant on the experience of the reader [149,150]. In order to gain competency at mpMRI interpretation, it is estimated that approximately 100 mpMRI reports, supervised by a double reader and validated by histopathology are needed [151]. Once competent, to maintain the required experience level it has been shown that a clinician needs to report a minimum of 50 mpMRI's per year [152,153]. Amongst experienced radiologists, PI-RADS v2 has demonstrated moderate reproducibility, with peripheral zone tumours easier to identify than transition zone cancers [154].

1.1.5.8.4 Prostate Cancer Diagnosis and mpMRI

Prostate mpMRI has several established clinical applications in prostate cancer. It was initially used to assist with surgical planning by helping to define the extent of disease prior to definitive treatment. Prostate MRI could help determine if there was extracapsular disease or seminal vesicle/neurovascular bundle involvement thus changing the disease stage and potentially the proposed treatment. Further roles for prostate MRI involve the diagnosis of primary prostate cancer.

Initial presentation with no prior biopsy

Increasing evidence suggests that prebiopsy MRI is a highly valuable addition to the diagnostic pathway. This update has been endorsed by a number of guidelines from expert groups including the European Association of Urology (EAU) [25] and the United Kingdom National Institute for Health and care Excellence (NICE) [155]. In the multicentre PROMIS trial, 576 biopsy naive men with an abnormal prostate exam, raised PSA or suspicious family history, underwent a prostate mpMRI prior to a standard TRUS biopsy and TP biopsy that formed the reference standard. Results showed that prostate mpMRI had a greater sensitivity (93%) than

TRUS biopsy (48%) for the detection of clinically significant cancer (cancer length ≥6mm or Gleason score ≥4+3) but less specificity (41% vs 96%). Biopsies in 27% of men may have been avoided missing only 5% of clinically significant cancer if PI-RADS score 1 and 2 lesions were not biopsied [156]. This study is somewhat limited by its era specific protocol, that mandated the use of a 1.5 Tesla MRI and relied on a now outdated 5-point Likert scale for prostate imaging reporting rather than the modern PI-RADSv2 rubric. Recently a Cochrane report investigated the best method for identifying clinically significant (ISUP≥2) prostate cancer in men who have never had a prostate biopsy or have had a previous negative biopsy. The different strategies that were reviewed included: MRI only, MRI-targeted biopsy, MRI pathway (MRI with or without MRI targeted biopsy) and systematic biopsy. They concluded that the MRI pathway represents a more favourable diagnostic test than systematic biopsy in men suspected of clinically significant prostate cancer [157].

Prior negative TRUS biopsy with elevated serum PSA

Prostate mpMRI has an established role in investigating high serum PSA levels in men who have previously had a negative TRUS biopsy [158,159]. Following a prostate MRI, biopsy targets are identified and can then guide a targeted biopsy. It has been shown that a targeted re-biopsy is better than systematic biopsies at identifying clinically important prostate cancer [160]. Up to 40% of men will have ISUP≥2 prostate cancer identified on MRI-targeted biopsy following an initial negative biopsy [157,161-163].

Men choosing active surveillance

For men eligible for active surveillance, prostate mpMRI adds value due to its high negative predictive value (83-95%). This provides further reassurance that ≥ISUP 2 prostate cancer has not been missed [164-166]. To further emphasize how prostate MRI can enhance patient selection for active surveillance, Ouzzane et al reviewed 281 men who were considered to be eligible for active surveillance. These men underwent a prostate mpMRI and 28 (10%) men were then excluded from active surveillance because clinically significant disease was identified [167]. In addition, prostate mpMRI scans are now widely accepted as a valuable component of active surveillance protocols [168-170].

1.1.6 Staging

Commonly prostate cancer is staged using the American Joint Committee on Cancer (AJCC) system [171]. Currently in its eighth edition, it combines three tumour variables: (1) the extent of the primary tumour (T) (2) if any lymph nodes have cancer involvement (N) (3) if distant metastasis are present (M) (Table 3). In combination with PSA and histologic grade group of the primary tumour, the AJCC also provides prognostic stage groups to classify men according to their risk of recurrence post prostatectomy (Table 4). Men can also be stratified into clinical risk categories that have been defined by the National Comprehensive Cancer Network (NCCN) (Table 5), that can then be used to guide further clinical evaluation. Men who present with a very high PSA level or have staging studies that are consistent with metastatic disease

are still require histopathological confirmation via a biopsy of either the prostate or a metastatic site. This is so the diagnosis can be confirmed and the patient can be assessed for suitable treatment options, such as if current or future clinical trials are appropriate.

Once prostate cancer has been confirmed by tissue diagnosis, there are a number of factors that guide the approach to staging. These include: life expectancy, symptoms, comorbidity and risk category. In general, men who have a <10-year life expectancy, are asymptomatic and have been diagnosed with low or very low risk cancer (NCCN) can be observed without further staging workup unless they develop symptoms or their disease progresses. For men with low-risk disease but a life expectancy >10-years or a higher risk cancer profile, additional staging is often indicated to identify possible metastatic disease. Prostate cancer most commonly metastasis to the patient's regional lymph nodes or bones, metastasis to other sites around the body is much rarer. Up to 40% of men with NCCN high risk prostate cancer have been shown to harbour lymph node metastases [172]. To further assess for extraprostatic extension or prostate cancer metastases expert groups recommend further investigation through imaging studies that may include: computer tomography (CT), abdomen/pelvis MRI, mpMRI of the prostate, technetium-99 radionuclide bone scan or newer imaging modalities such as highly sensitive radiotracers for integrated positron emission tomography (PET/CT) [25,74].

Primary tumour (T)	
Clinical T (cT)	
T category	T criteria
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour that is not palpable
T1a	Tumour incidental histologic finding in 5% or less of tissue resected
T1b	Tumour incidental histologic finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy found in one or both sides, but not palpable
T2	Tumour is palpable and confined within prostate
T2a	Tumour involves one-half of one side or less
T2b	Tumour involves more than on-half of one side but not both sides
T2c	Tumour involves both sides
T3	Extraprostatic tumour that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Pathological T (pT)	
T category	T criteria
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.
Note: There is no pathological T1 classification.	
Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residua, microscopic disease.	
Regional lymph nodes (N)	
N category	N criteria
NX	Regional nodes were not assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)
Distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease
Note: When more than one site of metastasis is present, the most advanced category is used. M1c is the most advanced.	

Table 3: Prostate cancer TNM staging AJCC 8th edition

The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. Corrected at 4th printing, 2018.

When T is…	And N is…	And M is…	And PSA is…	And Grade Group is…	Then the stage group is…
cT1a-c, cT2a	N0	M0	<10	1	I
pT2	N0	M0	<10	1	I
cT1a-c, cT2a, pT2	N0	M0	≥10<20	1	IIA
cT2b-c	N0	M0	<20	1	IIA
T1-2	N0	M0	<20	2	IIB
T1-2	N0	M0	<20	3	IIC
T1-2	N0	M0	<20	4	IIC
T1-2	N0	M0	≥20	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

Note: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

Table 4: Prostate cancer TNM prognostic stage groups AJCC 8th edition

The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. Corrected at 4th printing, 2018.

Risk group	Clinical/pathologic features
Very low	• T1c AND • Grade group 1 AND • PSA<10 ng/ml AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND • PSA density <0.15 ng/mL/g
Low	• T1 to T2a AND • Grade group 1 AND • PSA<10 ng/mL AND • Does not qualify for very low risk

Favourable intermediate	• No high or very high risk features
	• No more than one intermediate risk factor:
	  o T2b to T2c OR
	  o Grade group 2 or 3
	  o PSA 10 to 20 ng/mL AND
	• Grade group 1 or 2 AND
	• Percentage of positive biopsy cores <50%

Unfavourable intermediate	• No high or very high-risk features
	• Two or three of the intermediate risk factors:
	  o T2b to T2c
	  o Grade group 2 or 3
	  o PSA 10 to 20 ng/mL AND/OR
	• Grade group 3 AND/OR
	• ≥50% of positive biopsy cores

High	• No very high-risk features AND • T3a OR • Grade group 4 or 5 OR • PSA>20 ng/mL
Very high	• T3b to T4 OR • Primary Gleason pattern 5 OR • Two or three high-risk features OR • >4 cores with Grade group 4 or 5

Table 5: NCCN risk stratification criteria for localized prostate cancer
Adapted from: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prostate Cancer. Version 4.2018.

1.1.7 Population Screening

Population-based prostate cancer screening programs are controversial. They aim, through the detection of prostate cancer at an early stage, to reduce disease-specific morbidity/mortality.

Reviews of the published literature have found that prostate cancer screening may at most offer a small benefit in reducing prostate cancer mortality [173,174]. Of note, one of the largest studies to investigate prostate screening, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, showed that screening did not translate to a significant difference in cancer related mortality compared to a normal care control group. However, the negative results of this study are now widely discounted because so many patients randomized to the control arm underwent screening as part of their usual care [175,176]. In regards to prostate cancer screening on incidence, it may reduce a patient's risk of developing advanced-stage disease. The European Randomized Study of Screening for Prostate Cancer (ERSPC) recruited 76,813 men and over a median follow up time of 12 years, showed that the screening group had a lower cumulative incidence rate of metastatic disease (0.67%) than the control group (0.86%). This translates to a 30% reduction in relative risk of metastatic disease in the cohort of men that underwent screening [177].

The disadvantages of prostate screening include a number of quantifiable harms. Overdiagnosis of clinically insignificant cancer inflicts the risks of screening, diagnostic investigations and treatment onto patients. These include the risks of prostate biopsy and the unnecessary morbidity that stems from false positive results. Currently, Australia does not have a national PSA screening program for prostate cancer. Instead, the Australian Cancer Council recommends that the patient and clinician arrive at a shared decision following a risk/benefit discussion regarding the role of screening [10,178]. This is congruent with the Prostate Cancer Foundation of Australia position paper released in 2016 and endorsed by the Urological Society of Australia and New Zealand (USANZ). Specifically, for men at average risk of prostate cancer who decide to undertake PSA screening after informed consent, a PSA test should be performed every 2 years from age 50 to age 69 [179].

1.1.8 Conventional Management

Prostate cancer management should be individualized to the patient. Relevant variables that should be considered include their age, general health and suitability for treatment (including life expectancy) as well as their preference and attitude towards different therapies. Due to the wide variance in prostate cancer's natural history, ranging from indolent through to highly aggressive disease, risk stratification is vital. Staging, as discussed in section 2.6, can classify patients into prognostic categories that can be combined with the clinical situation to help determine the most appropriate management option.

Active surveillance is a curative management approach that is suitable for men who have a low risk of their prostate cancer progressing. Active surveillance does not involve any definitive therapy, aiming to avoid intervention related morbidity. Cancer progression is monitored via regular PSA tests, mpMRI scans and repeat prostate biopsies. Prostate mpMRI is a rapidly evolving tool to help with patient selection and monitoring in the active surveillance setting (see section 2.5.8.4). In addition, the patient's desire and ability to follow surveillance scheduling is an important variable to consider prior to commencing active surveillance.

Radiation can be used to treat prostate cancer. Radiation may be delivered to the patient externally (external beam radiotherapy) or internally (seed brachytherapy). Radiation energy damages cancerous and normal tissue DNA, however malignant cells lack the molecular mechanisms to self-repair and are destroyed [180]. Whole gland radiation therapy of the prostate is associated with a number of short- and long-term complications. Acute gastrointestinal toxicity is common and presents as either enteritis or proctitis, with patients reporting tenesmus, defecation frequency/urgency and abdominal cramping [181]. Long term gastrointestinal side effects, such as persistent diarrhea, rectal urgency or hematochezia, are less common [182]. Rectal ulcers, perforations and anal strictures are rare, presenting in 1-5% of men treated with >74 Gy radiation [183-185]. Acute urinary symptoms (dysuria, frequency, urgency) commonly occur but typically resolve within the four weeks following therapy completion [183,184]. Following radiation there is a risk of hemorrhage from either radiation proctitis or radiation cystitis, this risk is significantly higher in men who are anticoagulated [186]. Gastrointestinal bleeding is the most common variant and is typically self-limiting rarely requiring transfusion whereas radiation cystitis can cause life threatening persistent hemorrhage. Sexual dysfunction can occur after radiation treatment for prostate cancer. In modern studies, 30-45 percent of men who are potent prior to therapy become impotent after radiotherapy [187-189]. When used as a primary treatment option for intermediate risk prostate cancer, radiation therapy and radical prostatectomy have equivalent patient survival outcomes [190].

Radical retropubic prostatectomy is the definitive surgical option for localized prostate cancer. This operation can be undertaken with an open, laparoscopic or robot-assisted approach. The majority of radical proctectomies are now performed using robot assistance [191], with the purported advantage of the laparoscopic and robotic-assisted options being reduced intraoperative blood loss and a smaller incision. However, the superiority of less invasive approaches has not been demonstrated in the literature. Using the 'Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE)' database, 1137 men with localized prostate cancer who were treated with open radical prostatectomy were compared to 755 men with localized prostate cancer who were treated with robot-assisted prostatectomy. They found that oncologic outcomes were very similar for open and robot-assisted surgery with biochemical recurrence-free survival 87% verses 85% respectively and positive surgical margins 27% versus 24 % respectively. With both operative approaches, patients reported similar levels of urinary and sexual side effect three years post-surgery [192]. Importantly, the experience of the surgeon, regardless of approach, significantly impacts the outcome of this operation. Due to the significant learning curve for both open and minimally invasive prostatectomy, prior experience heavily correlates with better oncological outcomes [193,194]. Immediate complications specific to radical prostatectomy include rectal and ureteric injury and common long-term morbidity include urinary incontinence and sexual impotence. Urinary incontinence tends to improve over time with 90% of men considered to be continent at 6-24 months after their operation [195]. Sexual impotence is common in men who have undergone a radical prostatectomy, with most patients experiencing at least temporary erectile dysfunction even after nerve-sparing operations. Promisingly, bilateral nerve sparing techniques have

demonstrated potency rates up to 86% at two-year follow up in carefully selected men who also use phosphodiesterase inhibitors [196,197]. The rate of potency following radical prostatectomy without nerve sparing is significantly lower, one study of 173 men found that only 16% of men reported no erectile dysfunction after 12 years of follow up [198]. Prognosis following radical prostatectomy is heavily dictated by pathological stage however an analysis of 11,521 men with prostate cancer who underwent radical prostatectomy found that the overall 15-year prostate cancer specific mortality rate was 7% [199].

1.2 Focal therapy

1.2.1 Role for Focal Therapy

Modern imaging improvements have facilitated a widespread move towards tissue-preserving strategies managing cancer. A good example of this is the advent of minimal breast tissue resections, "lumpectomies," that have significantly improved the outcomes for breast cancer surgery. The terminology surrounding the use of focal therapy techniques to treat prostate cancer is not well defined. In current vernacular, the term 'focal therapy' in the context of prostate cancer management encompasses hemi-gland, quadrant and lesion specific techniques. In 2015 a consensus panel defined focal therapy as 'lesion targeted' therapy to treat specific areas of prostate cancer with the aim of less treatment related morbidity. This provided a distinction from non-targeted forms of focal therapy such as hemi-gland ablation, which were not clarified in the panel's definition [200]. However, this terminology has not been widely adopted and for consistency with the current literature, the term 'focal therapy' will be used as an umbrella term in this review. Numerous focal therapy modalities are available and will be discussed in section 3.2.

An optimised focal approach for prostate cancer treatment is still being determined. One recent systematic review analysed the clinical effectiveness of a primary focal approach for the management of localised prostate cancer and found no strong evidence supporting focal treatment compared to standard management [201]. The European Association of Urology (EAU) position paper on focal therapy (2018) laid out certain criteria that needed to be satisfied before primary focal therapy can become an accepted treatment modality [27]. In the setting of low-risk lesions that are amenable to active surveillance, focal therapy should be directly compared to active surveillance. For intermediate risk lesions that require active treatment, focal therapy should offer similar oncological results with less morbidity. The requirements that focal therapy should provide to patients as per the EAU position paper (2018) are (verbatim):

1. Survival efficacy at least equivalent to standard of care (SOC)
2. Fewer complications and functional side effects compared with SOC
3. Reliable follow-up of remaining prostatic tissue
4. Potential secondary or salvage treatment not impaired by the primary focal therapy

Detailed local staging is imperative for the selection of appropriate focal therapy candidates. Initially, it was men with low-risk disease and a healthy expectancy (>10 year) that were considered to be the target cohort [23,129]. However, as the validity of active surveillance continues to be emphasised in this patient group [190], the benefit of focal therapy for this group of men is unclear and may represent overtreatment. In response, the paradigm has shifted towards men with intermediate-risk prostate cancer now being considered the target focal therapy population. In 2015 an expert consensus panel endorsed the use of focal therapy for

intermediate risk prostate cancer and provided a number of parameters for patient selection, namely that candidate should have a life expectancy >5 years and a WHO performance status ≤1 [200]. In current clinical practice, in an investigational context, focal therapy occupies the middle ground between active surveillance and radical therapy, suggested suitable candidates include men with large, unilateral Gleason 6 cancer or small, unifocal Gleason 7 cancer [200,202].

1.2.2 Advances in Focal Therapy

1.2.2.1 Focal Therapy and the Index Lesion

Prostate cancer is predominately a multifocal disease [203,204] with unifocal lesions only present in an estimated 20% of patients [205,206]. As discussed in section 1.1.5.7, it is common for there to be one lesion of substantial size, identified as the 'index' lesion (Figure 8). As reported by Ohori et al, the index lesion accounts for up to 80% of prostate tumour volume [207]. Regarding the non-index lesions within the prostate, it is interesting to note that 80% of them have a tumour volume less than 0.5cm^3 [203]. Tumour volume of clinical significance is typically defined as >0.5cm^3 with a Gleason pattern >3 [203,204]. Using this definition, Rukstalis et al found in a cohort of 112 consecutive focal therapy (cryotherapy) cases that the mean volume of secondary lesion was 0.3cm^3 and that targeting the index lesion would likely eradicate 79% of clinically significant cancer [208]. One of the fundamental principles of focal therapy is that untreated and insignificant residual prostate cancer does not impact on long-term cancer control. Importantly, regardless of the presence of bilateral or unilateral cancer, risk stratification (tumour grade/tumour volume) and management of the index lesion dictates disease outcome [206]. This is because most prostate cancer metastases can be traced via genomic signatures to the index lesion [21,209]. Therefore, targeting the index lesion alone will theoretically provide oncological control to appropriately selected patients.

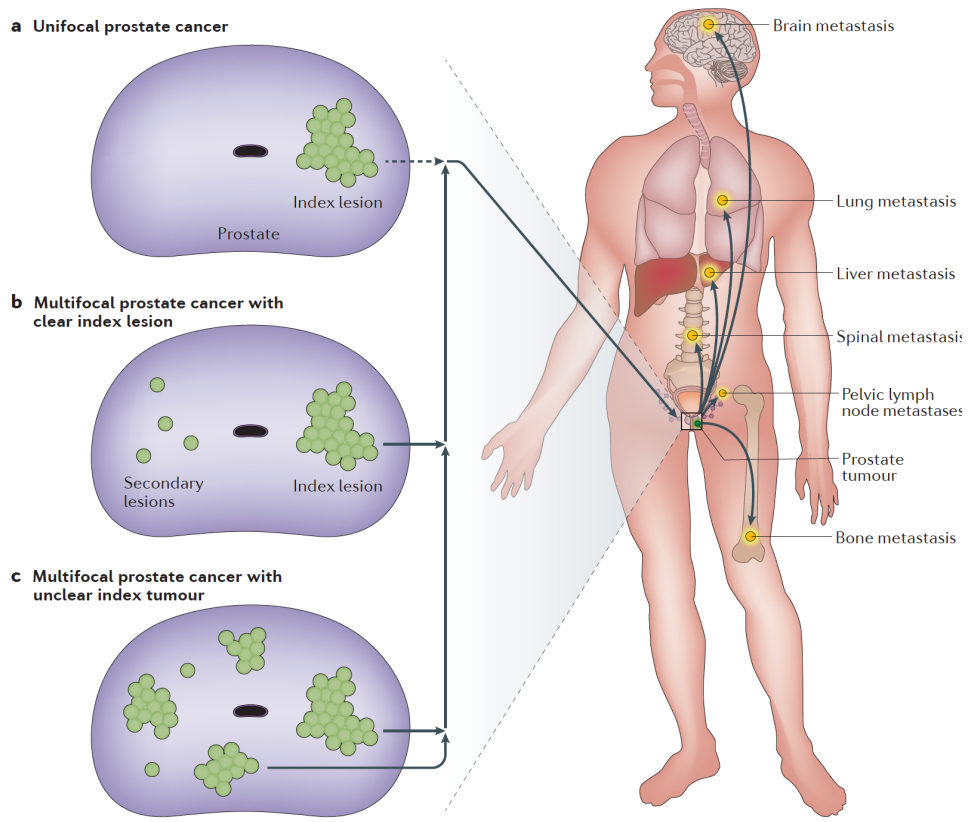

Figure 7: Metastatic properties of prostate cancer
a) Unifocal prostate cancer b) Multifocal prostate cancer with clear index lesion and separate secondary tumour foci with smaller volume (most common) c) Multifocal cancer with unclear index lesion.
Image obtained from "An update on focal therapy for prostate cancer", Perera et al 2016 [1].

1.2.2.2 Disease Localization

Focal therapy relies on the capacity to accurately localize and characterize prostate cancer so that only appropriate patients are selected. Prior to focal therapy, prostate cancer diagnosis is required via prostate biopsy (section 2.5.4). Standard 12-core TRUS biopsy alone is insufficient, underestimating tumour volume and disease risk [210,211]. Instead, TP prostate biopsy which allows for greater interrogation of the prostate is commonly performed [212]. This provides a histologic map of intraprostatic lesions. Ultrasound guided prostate biopsies should be performed in a systematic manner, sampling bilaterally from apex to base with adequate cores being taken from the anterior, mid and posterior areas of the prostate gland. Cores should also be taken as far lateral as possible in order to adequately sample the peripheral zone of the prostate, where prostate cancer is more likely to be identified. The European Association of Urology recommend at least 8 systematic biopsies in prostates up to 30cc, for larger prostates 10-12 biopsy cores are recommended. Additional cores should be taken from areas of the prostate considered to be at high risk for cancer based upon imaging or clinical results [25].

Advancements in imaging technology now allow for the size and position of suspected prostate cancer to be accurately determined by high quality mpMRI. Lesions that are identified can then

undergo a targeted biopsy, with his approach demonstrating increased histopathological concurrence with radical prostatectomy specimens [163,213]. However, it is worth noting that regardless of improvements in MRI image quality and interpretive skills, there are known limitations of MRI [214]. A recent meta-analysis found the combined sensitivity for the detection of clinically important cancers to be 74% [215]. In addition, Vargas et al compared clinically significant prostate cancers (Gleason score ≥4+3) and found seven out of 206 tumours had a PI-RADS 1 score, effectively making them invisible to mpMRI [216]. It has also been demonstrated that mpMRI can substantially underestimate tumour size which has particular relevance to focal therapy. This in part is relates to technical limitations with magnetic resonance imaging as well as tumour heterogeneity which makes differentiating normal tissue from cancer difficult [217]. Borofsky et al found at a second look analysis that lesion size was underestimated in 8 out of 100 patients [218]. The degree of cancer volume underestimation can be up to 9 mm [219], with tumours in the anterior region more often underestimated due to technical difficulty of MRI interpretation in the anterior fibromuscular and transition zones [220]. More specifically, Pooli et al compared the radiologic and pathologic tumor size of 461 lesions and found that the degree of underestimation increases with smaller tumours identified radiological and tumors with lower PI-RADS scores [221]. These factors should be taken into account when determining treatment margins for focal therapy.

1.2.2.3 Focal Ablation Strategies

For all focal therapy modalities, consensus guidelines recommend a number of ablative parameters for treatment. Based on the observation that a 2-3mm margin of error results in a 90-95% tumours with a volume of 0.5cm^3 being treated, clinicians should target a post treatment radiological margin of ≤5mm around the lesion (11). Current focal ablation techniques include: extended hemiablation “hockey-stick ablation”, hemiablation of unilateral prostate cancer or targeted focal ablation of the index lesion (Figure 9). In a systematic review (2014) of 2,350 focal therapy cases, 51% were treated with targeted focal therapy and 49% treated with hemiablation or extended hemiablation (28).

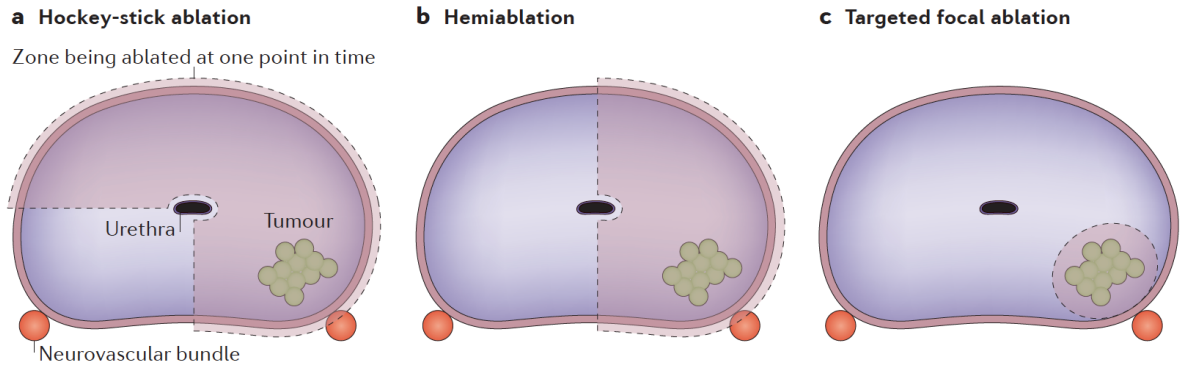

Figure 8: Different ablation strategies
a) Extended hemiablation "hockey-stick": involves hemiablation of the prostate cancer side plus the anterior or contralateral region b) Hemiablation: involves eradication of prostate cancer within a hemisphere of the prostate, depending on the location of the tumour, to the right or left of the urethra c) Targeted focal ablation: involves selective treatment of prostate cancer in a specific area of known tumour. Image obtained from "Image guidance for focal therapy of prostate cancer", Lindner et al 2010 [8].

1.2.2.4 Defining Treatment Failure and Success

Insufficient data has been published to determine how effective focal therapy is at treating prostate cancer in the long-term, in addition long term outcomes from randomised, prospective studies are not available in order to outline the best surveillance protocol post treatment Consensus recommendations from the Société International d'Urologic-International Consultation on Urologic Diseases recommend regular PSA testing (including density, nadir and other kinetics), re-look mpMRI at 6-12 months and a follow-up prostate biopsy at 12 months post treatment [222].Repeat prostate biopsies post treatment are essential to assess the effectiveness of focal therapy. Typical triggers for biopsy are: a rise in PSA level, suspicious finding on post treatment mpMRI or as dictated by the surveillance protocol. Interpreting post treatment biopsy results can also be challenging as residual disease may not be clinically significant. A 2015 report from a consensus meeting defined insignificant disease as '*biopsy result of Gleason score 3+3=6 in the treated area with cancer core lengths ≤3mm taken at one year post treatment*'. Whereas greater volume Gleason 3+3 or Gleason score 4+3 or 3+4 disease in the focal target area denotes treatment failure [200]. Additionally, recurrent prostate cancer may be classified as in-field or out-of-field based upon mpMRI and biopsy results. In-field failure refers to significant disease within the focal treatment area and reflects ineffectual treatment. Out-of-field disease is located outside the focal therapy ablation zone, in untreated prostate tissue, and represents de novo disease or selection failure if it, within 18 months.

Serum PSA monitoring can also be used as a surrogate marker for focal therapy success. Typically, definitions for PSA failure following focal therapy are based on prostate cancer radiotherapy guidelines such as the American Society Radiation Oncology (ASTRO) Phoenix criteria. According to this definition, a '*PSA rise of ≥2 ng/mL above the nadir PSA is considered a biochemical failure*' in a man who was previously treated with definitive RT, independent of androgen deprivation therapy (ADT). Although an increase in PSA of 2 ng/mL

or more is defined as a biochemical relapse, a repeat test is generally carried out to rule out a PSA bounce [223]. To date, no PSA monitoring criteria has been wholly endorsed for surveillance following focal therapy and there is an inherent challenge in interpreting PSA results post focal therapy when remaining viable prostate tissue still produces PSA. Intuitively, focal therapy success can be defined as the destruction of the targeted prostate lesion with preservation of non-cancerous native prostate tissue. What this means in terms of oncological outcomes is not well defined but retreatment rates of up to 20% following focal therapy have been deemed clinically acceptable by an expert consensus panel [200].

1.2.3 Types of Focal Therapy

There are a number of ablative focal therapy techniques currently being utilised. Regardless of the modality, ablation of the cancer is crucial. All of the different focal therapy modalities that will be discussed below have demonstrated their effectiveness in phase 1 clinical trials. Confirmation of successful treatment within the intended target zone and assessment of the impact on the surrounding tissue was confirmed by either the histopathological examination of a planned prostatectomy specimen several weeks after focal therapy or by targeted MRI-guided prostate biopsies of the treatment zone. Focal brachytherapy is the main focus of this thesis and will be discussed in detail in section 3.3.

1.2.3.1 Cryosurgery

Cryotherapy treats prostate cancer by freezing the targeted area under ultrasound guidance. This causes cell ischaemic apoptosis via destruction of cell membranes from ice crystals, protein denaturation and ischemia caused by frozen vasculature and microthrombi [224]. Cryotherapy was the pioneering prostate cancer focal therapy modality and quickly increased in popularity, with its use increasing 10-fold between 1999 and 2005 [225,226]. Using cryoprobes placed into the prostate transperineally under ultrasound guidance, an ice ball is formed when the probes are rapidly cooled. This ice ball can be monitored in real time using ultrasound but there are limitations to image quality given the reflective nature of the ice ball that need to be considered [227]. The effectiveness of the ablation is determined via intraoperative temperature checks that give feedback regarding the impact of the ice ball and the degree of healthy tissue preservation [228]. A recent technological innovation is the development of MRI-compatible cryoprobes [229] which allows for monitoring with greater accuracy [230]. To date, nine published series [226,231-238]have explored the treatment toxicity and oncological outcomes of focal cryotherapy, with the majority of these studies utilising a hemiablative focal approach [239]. Shah et al's systematic review of primary focal cryotherapy reported failure-free survival rate of 71-93% after 9-70 months of follow-up. Incontinence rates were 0-3.6% and erectile dysfunction affected 0-42% of men [240]. The wide range of reported erectile dysfunction likely reflects the heterogenous instruments used to assess sexual impairment.

1.2.3.2 High Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) was first described as a prostate cancer treatment in 1995 [241]. HIFU ablates targeted tissue through the use of high-powered ultrasound waves that typically exceed 5 Watts per cm^2. Tumour destruction occurs via two mechanisms, firstly ultrasonic energy is converted to heat causing coagulative necrosis and secondly the rapid growth and collapse of the generated bubble causes inertial cavitation [242]. Both of these physiological mechanisms can be utilised very precisely which allows for HIFU focal therapy to be highly accurate when targeting specific lesion. In clinical practice, HIFU is delivered via a transrectally placed ultrasound probe that allows for real-time imaging and distribution of HIFU energy to the desired location. Although, the TRUS probe is unable to determine the efficacy of treatment once ablation has begun. To mitigate potential HIFU overtreatment or overheating prostate tissue [243,244], MRI monitoring has been developed that provides constant temperature assessments and can track the treatment penumbra [245]. Most published data regarding oncological outcomes following HIFU therapy report rates of retreatment ranging from 0% to 34% [231,241,243,246-253].

1.2.3.3 Laser Ablation

Laser ablation can be used as a prostate cancer focal therapy modality. Prostate tissue is highly amenable to laser ablation as it has a high absorption capacity and limited conduction pathways that can reduce energy transference [254]. Laser ablation is very precise and initiates cell death by causing; areas of inflammation (hyaline fibrotic scars), hemosiderin deposits and coagulative necrosis [255]. Laser ablation therapy is administered via a laser probe which is accurately placed into the prostate transperineally under TRUS/MRI guidance. The evaluation of laser ablation treatment can then be monitored in real-time via TRUS/MRI and determines when adequate destruction of pathological tissue has been achieved [256-258]. This method of focal therapy has passed Phase 1 trials and consequent series have shown MRI guided focal laser ablation to be effective and safe [258-260]. To date, the largest study assessing focal laser ablation is currently ongoing however interim results have been published. Of the 98 patients and 138 tumours treated using real-time MRI laser ablation, 23% of patients had an in-field cancer recurrence. They report that there were no serious adverse events or documented urinary or sexual impairment recorded at 12-month review [261].

1.2.3.4 Photodynamic Therapy

Photodynamic therapy is a highly novel technique that involves intravenous administration of pharmacological agents that activate in the presence of light (photosensitisers) and destroy cancer cells [262]. Photosensitisers are relatively biologically inert and can be systemically administered to permeate the prostate. Focal treatment of prostate cancer is performed via lasers placed transperineally that emit light within a targeted area of the prostate as directed by TRUS guidance[263,264]. Following approximately 20 minutes of light exposure, photosensitisers propagate cytotoxic reactive oxygen species that cause cellular and vascular damage [265]. This

allows for the selective activation of photosensitisers enabling considerable local control over treatment zones. Initial studies conducted in the 1990 used photosensitising agents such as hematoporphyrin or polyporphyrin [265]. Subsequent modern trials tend to use WST-11 or WST-09 [266] photosensitisers. Both of these agents are triggered by light that has a low wave length, 753-757nm for WST-11 and 763 nm forWST-09. The low wave length light allows for better saturation of the target lesion. Future research areas include the development of prostate cancer targeting photosensitizing agents that may reduce periprostatic tissue damage and lower morbidity [267]. Other technological innovations in development include intraprostatic detectors that can monitor drug, light and oxygen concentrations intraoperatively improving treatment efficacy [268]. In 2018, Gill et al reported an update from their phase III randomised trial comparing active surveillance to photodynamic therapy. They found in a cohort of 413, evenly randomised to each group, that 25% of the treatment arm had residual disease in the treatment field. In addition, they showed that patients in the phototherapy group proceeded to radical therapy less frequently than in the active surveillance group (24% vs 53 % respectively, hazard ratio 0.31, 95% confidence interval 0.21-0.45). Although more men in the control arm underwent radical treatment without a clinical indication, confounding this finding. Also, somewhat expectedly adverse effects occurred more commonly in men who received photodynamic therapy compared to active surveillance, with a higher rate of erectile dysfunction (38% vs 11% respectively) and urinary symptoms (27% vs 7% respectively) [269]. Similar to other focal therapy modalities, the long-term oncological evidence for photodynamic therapy needs to mature.

1.2.3.5 Irreversible Electroporation

Irreversible electroporation (IRE) uses short electrical pulses to ablate the selected prostate tumour. High-voltage electrical currents are delivered via three to six transperineally inserted electrodes causing cell membrane destabilization and cell death of the targeted tissue. The IRE ablation zone is invisible to TRUS guidance which creates targeting tissue difficulties, although utilising contrast-enhanced US and mpMRI techniques have shown promising results [270,271]. Amongst contemporary focal therapy techniques, IRE is the most novel with the first human studies in localised prostate cancer conducted in 2014 [272]. As yet, no randomised control trials assessing IRE compared to standard treatment have been completed. Blazeveski et al published the largest prospective cohort study, they included 123 patients who underwent IRE for mostly intermediate risk prostate cancer and reported on outcomes at a median follow-up of 3 years. Importantly they found IRE to be safe, with no reported Clavien-Dindo Grade III-IV adverse effects. They showed that failure-free survival, defined as avoidance of metastasis, death or whole gland therapy, to be 96.75% at three years follow up. Strikingly, their initial rate of in-field recurrence at 12-month TP prostate biopsy was 16%. This rate decreased to 2.7% when the treatment margin was enlarged from 5 to 10 mm and the surgeon gained more experience [273]. IRE is a promising focal ablative modality that has demonstrated effective short-term oncological control with limited treatment toxicity in carefully selected men diagnosed with localised prostate cancer. It should be considered an investigational treatment that is only

undertaken as part of prospective clinical registry studies or randomised trials until more comprehensive data are available [274].

1.2.4 Focal Brachytherapy

Brachytherapy uses radioactive seeds placed into the prostate as a therapeutic modality. Using carefully constructed radiation maps, seeds can be placed so that high radiation dosages are limited to the prostate. Whole gland brachytherapy is an established treatment option for localised prostate cancer [275-277] and is considered to be a standard of care option for low to intermediate localized prostate cancer. Radiotherapy techniques have well established biological mechanisms for tumour ablation (Section 2.8) with validated dose-dependent relationships to titrate therapy [278]. As with all focal therapy, focal brachytherapy aims to obliterate the targeted lesion while maintaining as much healthy tissue as possible in order to limit treatment morbidity. This is achieved via accurate and well-planned brachytherapy seed placement, guided by prebiopsy mpMRI and diagnostic prostate biopsy results. By concentrating seed density within the prostate cancer index lesion, studies have confirmed successful treatment effect across the whole targeted area[279]. In addition, Al-Qaiseh et al demonstrated focal brachytherapy reduced radiation exposure to adjacent organs compared to whole gland brachytherapy [280].

Currently, there are several published studies that report oncological outcomes following lesion targeted LDR brachytherapy [18,231,281-284]. The accumulated number of patients included in these studies is 115 with a median follow-up time of 17 months. As such, there is a critical need for more data in order to evaluate this treatment modality further. Cosset et al investigated the feasibility and toxicity of targeted focal brachytherapy treating 21 men with localised prostate cancer. They achieved good dosimetry results, using an undefined 'large safety margin' targeting a mean tumour volume of 13.7 cm^3 (range 7.0 – 22.5). This translated to a mean PSA value drop of 3.2 ng/ml at 6 months. At the time of publication only 28% of patients had undergone their post-implant biopsy and no significant cancer was identified. Additionally, patient-reported quality of life outcomes were found to be similar when compared to a matched whole gland brachytherapy cohort [281]. Building on this data, Graff et al completed an IDEAL 2a Phase II study of 17 men with low-to-intermediate risk prostate cancer, with most patients (13/17) enrolled with Gleason Score 3+3 cancer. They reported good oncological results with benign surveillance mpMRI and repeat prostate biopsy results at one-year post-implant in 16 patients (94%). One patient had a positive repeat mpMRI scan with a new lesion identified away from the treatment zone that on biopsy was shown to be significant cancer. He proceeded to have an uncomplicated radical prostatectomy [18]. Importantly, this patient's PSA had declined from 8.1 to 3.9 ng/mL following treatment, illustrating the importance of collaborative multimodal post-focal therapy follow-up. The cumulative incidence of biochemical recurrence post-focal LDR brachytherapy has been shown to be 0% at 1 year across multiple studies [18,281,283,284]. Kunogi et al reported longer follow-up and found the incidence of PSA relapse at 2 years to be 7.1% (1/14 patients) [284]. In this analysis, disease control was assessed by repeat mpMRI with no patient undergoing a follow-up prostate biopsy. While these preliminary

results are encouraging, further studies with longer oncological assessment, including biochemical and histologic surveillance, are needed to determine the real efficacy of focal LDR brachytherapy for low-to-intermediate risk prostate cancer.

1.2.4.1 Technique

Brachytherapy allows for high radiation doses to be given directly to the target area, effectively treating prostate cancer from the inside. It is more convenient for the patient than external beam radiation therapy, which requires five treatments per week for seven to eight weeks. Brachytherapy using permanent prostate implantation is typically completed as day procedure. One of the greatest hurdles stopping prostate cancer brachytherapy from becoming more widespread is the limited number of skilled practitioners who are capable of performing the procedure. In Australia, the performance of prostate brachytherapy typically requires both a trained radiation oncologist and urologist to be present.

During prostate brachytherapy, the radiation sources are accurately introduced via transperineal needles using TRUS imaging and stabilised via a fixed template to control needle position. This can be performed under sedation or general anaesthetic. Radiation can be delivered via permanent low dose rate (LDR) radioactive seeds or via temporary high dose rate (HDR) sources into hollow catheters/needles that have been positioned in the prostate.

LDR brachytherapy uses a computerized treatment plan to permanently embed approximately 75 to 125 (depending on prostate size) radioactive seeds withing the prostate. The planned radiation therapy dose is emitted over several months, with variation pertaining to the specific isotope selected [285]. Popular seeds include palladium-103 (Pd-103) and iodine-125 (I-125), with no reported superiority of one isotope over the other [286-288]. The prescribed dose to the target lesion has varied across studies, typically 145-180 Gy is considered to be the optimal dosimetry of focal LDR brachytherapy [280,289,290].

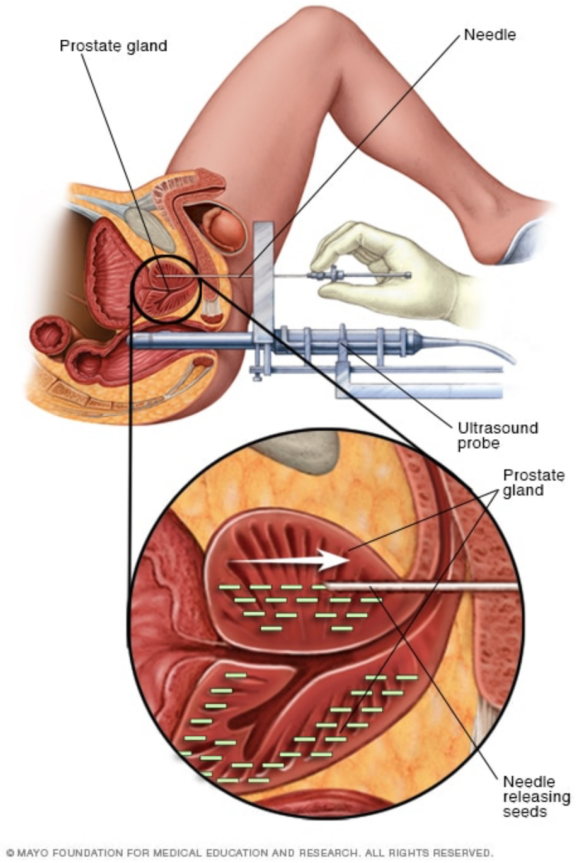

Figure 9: Whole gland prostate brachytherapy
Image illustrates whole gland brachytherapy seed placement. Graphic obtained from Mayo Clinic 'Brachytherapy' material. © Mayo Foundation for Medical Education and Research (MFMER). All rights reserved, 1998-2021.

HDR brachytherapy involves the placement of template guided transperineal catheters, through the perineum and into the prostate based on a treatment plan determined by previous imaging. These hollow tubes are then loaded with an isotope such as iridium-192 (Ir-192) that is able to provide a maximal radiation dose approximately 1000-fold greater than LDR brachytherapy. The HDR brachytherapy treatment is usually administered in 1-4 large dose fractions, typically over 24-40 hours. When patients are prescribed more than one fraction, they remain in hospital with the perineal catheters in situ until treatment is completed. Although some studies suggest that HDR is associated with slightly lower genitourinary morbidity than LDR, due to a more rapid drop-off in radiation dosing at the edge of the gland, most studies do not support a clear advantage of one technique over the other [291-294].

1.2.4.2 LDR Brachytherapy Toxicity

Focal LDR brachytherapy aims to limit the biological impact on a patient's urinary and sexual function by preserving non-cancerous prostate tissue, sparing the neurovascular bundles, bladder neck and urethra. Focal brachytherapy has reported similar or slightly better urinary toxicity profiles compared to whole gland brachytherapy. Using Common Terminology Criteria for Adverse Events (CTCAE), Tanaka et found 67% of men following LDR whole gland brachytherapy reported urinary toxicity (any grade) [295]. Of note, whole gland brachytherapy also carries a 5-10% risk of late severe urinary toxicity (≥ grade 3) [289,296]. Most of the reported urinary toxicity following focal brachytherapy appears to occur in the initial

two to six months following treatment and then resolves to near baseline by the 12 months [281,282]. Further, Prada et al reported an improvement in mean International Prostate Symptom Score (IPSS) score at 12 and 24 months following focal brachytherapy, potentially caused by a decrease in prostate volume after treatment improving obstructive urinary symptoms [297]. The anatomical location of focal brachytherapy seeds might also predict the likelihood of worse urinary function. The bladder trigone, at the prostate base, when injured or irritated by radiation has been shown to intensify urinary symptoms in whole gland brachytherapy [298 299]. Srougi et al corroborated this finding with focal brachytherapy, finding significantly more urinary toxicity in patients who had seed placement at the prostate base rather than the apex [282]. Additionally, early urinary toxicity, namely acute urinary retention, is associated with increased number of needles used in whole gland brachytherapy [300]. Presumably, more needle punctures of the prostate equate to greater prostate oedema and a higher likelihood of mechanical obstruction of the urinary system.

To date, clinical toxicity data regarding erectile impairment is mostly available from small studies with notable heterogeneity in the evaluation of measurement and outcome. Nevertheless, studies suggest that there is only a small impact on erectile function when compared to baseline. Maenhout et al showed in a cohort receiving high dose focal brachytherapy that 11 out of 30 patients had worse erectile function after treatment, with 73% reporting only a slight deterioration compared to baseline after one year [301]. Further, Cosset et al reviewed a case series of 21 men who received LDR focal brachytherapy and found the mean IIEF5 from a baseline of 20.1, at 6 and 12 months to be 19.1 and 19.5 respectively. When matched to a whole gland brachytherapy cohort, the focal group had a significantly faster recovery of International Index of Erectile Function (IIEF-5) score [281]. Likewise, Graff et al found in a prospective phase II trial of LDR focal brachytherapy in 17 men that there was no difference in IIEF5 score at baseline vs 1, 3, 6 and 12 month assessments [18]. By comparison, the rate of erectile dysfunction following whole gland LDR brachytherapy is reported at approximately 50% [302,303]. It has also been well established in the whole gland brachytherapy literature that having better erectile function before treatment increases the likelihood of retaining function after treatment [304,305], this correlation is likely to be valid for focal brachytherapy as well.

2. Research Formulation

2.1 Research Question

What is the 'viability' and 'feasibility' of lesion-targeted focal LDR brachytherapy as the primary treatment for low-to-intermediate risk prostate cancer?

Viability encompasses oncological, functional and salvage outcomes and feasibility contains to technical and procedural variables.

2.2 Research Statement

Focal therapy is an evolving treatment modality for men with prostate cancer who meet specific criteria. LDR brachytherapy can be used to target specific cancer lesions, ablating the tumour while leaving healthy prostate tissue untouched and limiting treatment related morbidity. This thesis will broadly explore focal LDR brachytherapy used as primary treatment for low to intermediate risk prostate cancer. Specifically, the completion of these projects should provide the foundation for a future comparative assessment study.

2.3 Research Design

This project has three components. Each project has its own study design with specific aims that integrate to provide a different but compatible analysis of the topic. Specifically, 'Project 1' formed the foundation for 'Project 3', with 'Project 2' investigating an important therapy question for focal LDR brachytherapy.

2.3.1 Project 1

Study Design
Retrospective cohort study, IDEAL Framework Stage 2a 'Development'[306]. This stage aims to investigate safety, technical and procedural outcomes to further develop the intervention.

Primary Objective
The primary objectives of this study are to determine:

- The oncological outcomes in this retrospective cohort, including PSA remission, biochemical recurrence and histopathology interrogation of the target lesion and the prostate gland post treatment.
- The toxicity profile and reported adverse events following focal LDR brachytherapy.
- Dosimetry outcomes and analytics for focal LDR brachytherapy as well as technical considerations for real world treatment implementation.

2.3.2 Project 2

Study Design
Case report, IDEAL Framework Stage 'Proof of Concept' [306].

Primary Objective
The primary objective of this study is to outline:

- The feasibility and technical challenges associated with salvage radical prostatectomy necessitated by biochemical failure following focal LDR brachytherapy.

2.3.3 Project 3

Study Design
Prospective, single institution but multi-centre clinical registry 'LIBERATE', IDEAL Framework Stage 2b 'Exploration' [306]. This stage seeks to provide a bridge from observational to comparative evaluation, gathering data for the future undertaking of a randomised control trial.

Primary Objective
The primary objectives of this study are to determine:

- The rate of 18-month local disease control, and
- The rate of 5-year biochemical progression-free survival following focal LDR brachytherapy in men with low to intermediate risk PCa.

Secondary Objective
The secondary objectives of this registry are to:

- Determine the toxicity profile of focal LDR brachytherapy.
    - Particularly in the domains of urinary, gastro-intestinal and sexual function.
- Measure the change in patient-reported generic and disease-specific quality of life.
- Determine the rate of 3-year biochemical progression-free survival.
- Determine the rate of salvage treatment.
- Determine the rate of complications following salvage treatment.
- Determine the rate of biochemical failure after salvage treatment.

2.4 Impact of COVID-19 pandemic

The COVID-19 pandemic has significantly impacted this research endeavour. Specifically, the recruitment of patients to Project 3 was greatly hindered by: mandated government surgical operating restriction, community lockdown restrictions and global supply chain disruptions. This pandemic has caused an unprecedented disruption to society, resulting in less cancer diagnosis and less treatment referrals [307]. Our initial enrolment projection was for 100 patients to be recruited within 25 months of LIBERATE opening. Given the limitations imposed by

COVID-19 this was not achievable and our protocol was amended based on modelling studies to allow for enrolment completion by 60 months after the registry opened.

3. Research Projects

3.1 Project 1

3.1.1 Introduction

Low dose-rate brachytherapy can be used as a lesion-targeted focal therapy, however, there is limited evidence to support its use and further studies are urgently required. This retrospective study contributes important data in a time when focal brachytherapy is becoming more widely used, but prospectively collected data continue to mature and are not yet ready to be published.

This is a multidisciplinary study, drawing on recent advances in cancer imaging, image-guided biopsies and precision radiotherapy treatment delivery. To our knowledge, this is the largest study specific to lesion-targeted focal brachytherapy to report on dosimetry, toxicity and oncological outcomes, and has the longest median follow-up in regard to cancer control.

The following manuscript forms Project 1 and was published in the *Journal of Translational Andrology and Urology*, September 2021.

3.1.2 Manuscript

Focal low dose-rate brachytherapy for low to intermediate risk prostate cancer: preliminary experience at an Australian institution

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3.1.2.1 Abstract

Background: Focal treatment for prostate cancer is a hybrid approach combining ablative treatment of the involved prostate gland and continued active surveillance of the unaffected gland. Low dose-rate (LDR) brachytherapy can be used as a lesion-targeted focal therapy, however, further studies are required to support its use. The aim of this study is to evaluate the dosimetry, toxicity and oncological outcomes of men receiving lesion-targeted focal LDR brachytherapy for low to intermediate risk prostate cancer.

Methods: This is a retrospective cohort study of twenty-six men with unifocal, low to intermediate grade PCa diagnosed on a combination of multiparametric-MRI and targeted plus

template transperineal biopsy, who received focal LDR brachytherapy at a single institution. Brachytherapy involved a single monotherapy implant using iodine-125 seeds to deliver a prescribed dose of 145 Gy to the index lesion.

Results: The mean focal planning target volume as a percentage of the prostate volume was 24.5%. The percentage of the focal gross tumour volume receiving 100% of the prescription dose was 100% for 12 patients and ≥98% for 18 patients. The median follow-up for toxicity and biochemical control outcomes was 23.1 (IQR 19.1–31.3) and 24.2 (IQR 17.9–30.0) months, respectively. Grade 2 urinary and erectile toxicities were reported by 29.2% and 45.8% of patients, respectively, with resolution of urinary symptoms to baseline by last follow-up. There were no grade ≥3 urinary or erectile toxicities or grade ≥2 rectal toxicity. All 21 patients who underwent a repeat multiparametric-MRI and transperineal biopsy at 12–24 months post-treatment were negative for clinically significant disease and 25 (96.2%) patients were free from biochemical failure.

Conclusion: Focal LDR brachytherapy is associated with a favourable toxicity profile and a high rate of control of significant prostate cancer at 12-18 months post-treatment. We have commenced the LIBERATE prospective registry in focal LDR brachytherapy based on the highly encouraging outcomes of this initial experience.

Keywords:
Brachytherapy, focal therapy, magnetic resonance imaging, prostate cancer

Ethical Statements:
The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate*: This retrospective study was approved by the Monash Health Human Research Ethics Committee (RES-20-0000-884L). The requirement* for consent was waived *by the Monash Health Human Research Ethics Committee* given the retrospective nature of this study.

Availability of data and material: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interests*: All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.*

3.1.2.2 Introduction

Prostate cancer (PCa) is the most common malignancy in men, contributing 25% of all new cancer cases and 12% of all cancer-related deaths in Australian males in 2019 [10]. Organ-confined PCa is typically managed with radical prostatectomy (RP) or radiation therapy which target the entire prostate gland and are associated with substantial impairment to erectile, urinary and bowel function [13,14]. To avoid or delay morbidity from treatment, men with low to intermediate risk PCa may be placed on an active surveillance (AS) protocol, reserving definitive treatment until disease progression has been identified by routine monitoring. The main drawbacks of AS are the potential to miss the opportunity for curative treatment and the substantial psychosocial stress associated with living with untreated PCa [15].

Focal therapy has emerged as a hybrid approach which involves ablative treatment of the involved prostate gland and continued AS of the unaffected gland [308]. Therapies described as focal for PCa can range from treatment targeted specifically to the lesion only up to any treatment that is to less than the whole gland, such as hemi-gland ablation [309]. However, as described in our series below, it is the lesion-targeted approach that takes advantage of recent advances in cancer imaging, image-guided biopsies and precision treatment delivery [17].

Scardino et al. [310], supported by the histopathologic observations of Ohori et al. [207], first proposed that targeted ablation of the "index" (or largest) PCa lesion might be sufficient for PCa control. This hypothesis is further supported by genomic analyses suggesting a monoclonal heritage for lethal metastatic disease [21], even though PCa is typically multifocal at presentation. Therefore, focal treatment of the index lesion, assuming that all other non-index lesions are low-grade, should be as effective as treating the whole prostate but with far less toxicity [1].

A variety of modalities, including high intensity focussed ultrasound, cryoablation, and photodynamic therapy are currently being investigated to deliver focal therapy for PCa [1]. Radiotherapy in the form of low dose-rate (LDR) brachytherapy has also been adopted given its well-recognised place as a standard option for whole-gland treatment of low to intermediate risk PCa [311].

Despite the increasing uptake of focal therapy for PCa across the globe, including LDR brachytherapy, robust evidence to support its efficacy and optimal utilisation is still maturing and further studies are urgently required [27]. Data specifically for lesion-targeted focal LDR brachytherapy is particularly lacking, with only six small studies (total of 115 patients) published to date (Table 1) [18,231,281-284].

This study reviews our initial experience with focal LDR brachytherapy for low to intermediate risk PCa, adding important oncological and toxicity data to the existing literature in this field and providing a preview of our subsequent prospective registry. We present the following article in accordance with the STROBE reporting checklist.

Table 1 Summary of focal LDR brachytherapy studies

Study (reference)	No. patients	Inclusion criteria	Follow-up (months)	Px dose (Gy)	Target size	Post-implant dosimetry	Oncological outcomes	Toxicity results
Barret *et al.* (2013) (14)	12	≤ cT2a; PSA <10 ng/mL; Gleason sum ≤6 (unilateral disease, <3 positive cores)	Median [IQR]: 9 [6–15]	145	NR	NR	PSA, median [IQR] (ng/mL): Baseline: 6.2 [5.4–7.5] 12 mo: 2.8 [1.2–4.7]	IPSS score, median [IQR]: Baseline: 3 [1–7] 12 mo: 7 [2–12] IIEF-5 score, median [IQR]: Baseline: 21 [10–25] 12 mo: 14 [8–24]
Cosset *et al.* (2013) (15)	21	cT1 or cT2a; PSA <10 ng/mL; Gleason score ≤3+4 (unilateral disease; no individual biopsy core with >50% involvement, <25% involved cores, total number of biopsies >20, systematic biopsy); prostate volume <60 cc; IPSS ≥15	Biopsy, median [range]: 18.5 [14–27] PSA: 12 mo for n=11	145	F-PTV, mean (range): 13.7 cc (7–22.5 cc)	F-PTV, mean (range): V100%: 99.3% (98.8–100%) D90%: 183.2 Gy (176.4–188.1 Gy)	PSA, mean [range] (ng/mL): Baseline: 6.9 [3.6–13.9] 12 mo: 2.6 [0.8–5.2] Repeat biopsy (n=6, 14–27 mo): Negative: n=5 Insignificant cancer: n=1	IPSS score, mean [range]: Baseline: 5.4 [0–15] 2 mo: 11.8 [1–28] 12 mo: 6.1 [2–9] IIEF-5 score, mean [range]: Baseline: 20.1 [5–25] 2 mo: 18.6 [5–25] 12 mo: 19.8 [5–25] GI (CTCAE) nil at 6 and 12 mo
Srougi *et al.* (2017) (16)	41 n=28 (apex) n=13 (base)	Life expectancy greater than 10 years; ≤ cT2a; PSA ≤15 ng/mL; Gleason score ≤3+4 (unilateral disease; no individual biopsy core with >50% involvement, <25% involved cores); prostate volume <60 cc	NR	145	F-PTV, mean Apex: 11.9 cc Base: 14.1 cc	F-PTV, median: V100%: 99.7% D90%: 182 Gy (apex), 183 Gy (base)	NR	IPSS score, mean: Baseline: 4.9 (apex), 6.3 (base) 6 mo: 6.4 (apex), 10.6 (base) 12 mo: 5.1 (apex), 7.6 (base) 24 mo: 6.2 (apex), 6.2 (base) IIEF-5 score, mean: Baseline: 19 (apex), 18 (base) 6 mo: 14.7 (apex), 16.3 (base) 12 mo: 16.5 (apex), 16.2 (base) 24 mo: 17 (apex), 16.5 (base)

Table 1 (*continued*)

Table 1 (*continued*)

Study (reference)	No. patients	Inclusion criteria	Follow-up (months)	Px dose (Gy)	Target size	Post-implant dosimetry	Oncological outcomes	Toxicity results
Mahdavi *et al.* (2017) (17)	5	≤ cT2a; PSA ≤10 ng/mL; Gleason score ≤3+4 (unilateral disease, ≤2 positive cores)	PSA, (range): 6–30 Toxicity, (range): 18–21	145	F-PTV, mean (range): 10.0 cc (5.5–12.9 cc)	F-CTV, mean (range): V100%: 90.4 (84.3–94.0)	PSA: declining post-treatment. Biopsy: n=2 negative/radiation effects at 24 mo	IPSS: nil change from baseline ED (SHIM): nil change from baseline
Graff *et al.* (2018) (18)	17	cT1-cT2a; PSA ≤10 ng/mL; ISUP Grade Group 1 (≤3 positive cores), no individual biopsy core with >50% involvement); prostate volume <60 cc; IPSS <10	12 (all endpoints)	160	F-GTV, mean (95% CI): 0.7 cc (0.6–0.9 cc)	F-GTV: D100% ≥95% in 16/17 patients	mp-MRI: Negative: n=16 PIRADS4: n=1 Repeat biopsy: Target: Fibrosis: n=15 Radiation effects: n=2 Template: Insignificant cancer: n=7 Negative: n=9 Significant cancer: n=1 (ISUP Grade Group 2)	GI (CTCAE): nil GU (CTCAE): Grade 1, n=1 Grade 2, n=2 IPSS: nil change from baseline IIEF-5: nil change from baseline
Kunogi *et al.* (2020) (19)	19	≤ cT2; PSA ≤15 ng/mL; Gleason score ≤7; no prior radiotherapy to pelvis, tumour concordant on mp-MRI and prostate biopsy.	Median (range): 31 [12–67]	145	F-GTV, mean (SD): 2.8 cc (2.7)	F-GTV, mean (SD): D90%: 222 (90.5) Gy	PSA: 2-year FFBF =92.9% mp-MRI (n=14): Negative: n=13 Recurrence: n=1	GU (CTCAE): 12 mo: n=3 Grade 2 24 mo: n=2 Grade 2 GI (CTCAE): nil reported
Current study	26	cT1c or cT2a; PSA ≤15 ng/mL; ISUP Grade Group 1 (≥10 mm in ≥1 core) or Grade Group 2 (longest core <15 mm); tumour concordant on mp-MRI and prostate biopsy.	Median [IQR]: PSA: 24.2 [17.9–30.0] Biopsy: 18.4 [12.9–19.3] Toxicity: 23.1 [19.1–31.3]	145	F-GTV, mean (SD): 3.8 cc (4.4) F-PTV, mean (SD): 10.8 cc (6.0)	F-GTV, mean (range): V100%: 93.2 (24.2–100) D90%: 237.6 (50–541.4)	PSA: FFBR: 18/18 at 18 mo 13/13 at 24 mo n=1 failure at 30.6 mo Repeat biopsy (n=21): Target: Radiation effects: n=19 Negative: n=2	GU (CTCAE): Acute (≤3 mo): n=7 Grade 2 Late (>3 mo): n=4 Grade 2 GI (CTCAE): Acute (≤3 mo): nil Late (>3 mo): n=4 Grade 1

Table 1 (*continued*)

Table 1 (*continued*)

Study (reference)	No. patients	Inclusion criteria	Follow-up (months)	Px dose (Gy)	Target size	Post-implant dosimetry	Oncological outcomes	Toxicity results
							Template: Negative: n=18 Insignificant cancer: n=3 mp-MRI (n=22): Negative: n=7 PIRADS2: n=14 PIRADS4: n=1, not significant cancer on biopsy	

LDR, low dose-rate; IQR, interquartile range; PSA, prostate-specific antigen; F-PTV, focal planning target volume; V100%, volume receiving 100% of the prescribed dose; D90%, dose to 90% of the structure volume; F-GTV, focal gross tumour volume; D100%, dose delivered to 100% of the ultrafocal gross tumour volume; PIRADS, prostate imaging-reporting and data system; SD, standard deviation; CTCAE, Common Terminology Criteria for Adverse Events; FFBF, free from biochemical failure; mp-MRI, multiparametric-magnetic resonance imaging.

3.1.2.3 Methods

Study design and patients

This is a retrospective analysis of the electronic medical records of men who were treated with focal LDR brachytherapy between August 2015 and December 2019 at a single institution. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). *The study was approved by the Monash Health Human Research Ethics Committee (RES-20-0000-884L). The requirement* for consent was waived given the retrospective nature of this study.

Twenty-six consecutive patients were included in the analysis. Patients eligible for focal LDR brachytherapy were aged 50 to 85, with a life expectancy greater than 10 years based on comorbidities not related to PCa and with no significant obstructive urinary symptoms. Eligible patients presented with clinical stage T1c or T2a disease, a serum PSA level ≤15 ng/mL and a lesion visible on multiparametric magnetic resonance imaging (mpMRI) with a Prostate Imaging-Reporting and Data System (PIRADS) score of 3–5 or a suspicious lesion on a ^{68}Ga-prostate specific membrane antigen positron emission tomography (^{68}Ga-PSMA-PET) scan. In addition, patients were required to have a reproducible target plus template transperineal (TP) biopsy of the prostate gland demonstrating a histologically proven index lesion of adenocarcinoma with ISUP Grade Group 1 (≥10mm in ≥1 core) or Grade Group 2 (longest core <15mm) coincident with the radiologically visible lesion, and either no cancer, or clinically insignificant cancer (ISUP Grade Group 1 with core length <10mm), in the remaining prostate gland.

Pre-treatment staging

MRI images were captured using a 3.0 Tesla MRI machine under PIRADS v.2 conditions. Multiple sequences were obtained, including T2-weighted images in axial, coronal and sagittal planes, axial and sagittal diffusion-weighted images including ADC map and high B-value of 1400 s/mm^2 and T1-weighted images of the pelvis. An axial dynamic contrast enhancement series was captured where available. All images were reviewed by an experienced radiologist who at a minimum reported on prostate size, total PIRADS score, extracapsular extension status, and size and location of all lesions.

Diagnostic TP biopsies were performed under general anaesthetic using a conventional 5 mm brachytherapy template grid and transrectal ultrasound (TRUS) probe. Identified MRI lesions were targeted with cognitive fusion and template cores were taken using the Ginsburg protocol [312]. All biopsy samples were double-read by experienced uropathologists.

Focal LDR brachytherapy

Focal LDR brachytherapy was delivered via a standard three-phase implant technique: pre-planning seed distribution, seed implantation and analysis of the dosimetric outcomes approximately 30 days post-implantation.

All patients underwent a pre-plan volume study using TRUS two weeks prior to their treatment. This enabled identification of the pubic arch, urethra and rectum allowing for better seed placement and reduced toxicity. Fusion of the patient's pre-planning ultrasound and their pre-biopsy mpMRI was performed for contouring using the fusion module within VariSeed (Varian Medical Systems, Palo Alto, CA) by a senior radiation oncologist and verified by a senior radiation therapist or radiation oncology medical physicist. The focal gross tumour volume (F-GTV) was the radiological extent of the index lesion, defined by a Boolean addition of the areas of abnormality observed on the different mpMRI sequences captured and the ^{68}Ga-PSMA-PET scan, if performed. The planning target volume (F-PTV) was a 7 mm isotropic expansion of the F-GTV to account for systematic uncertainties inherent within imaging modalities and post-acquisition image manipulation including fusion. For posteriorly located lesions adjacent to the rectum, the posterior GTV-PTV expansion was 0 mm. Eighteen men, all of whom had posterior index lesions, also received a SpaceOAR® (Boston Scientific, Malborough, MA) gel implant between the anterior rectal wall and whole prostate.

Table 2 Patient characteristics

Characteristic	N (%)
Age: mean (SD)	71 (5.6)
Clinical stage	
T1c	17 (65.4)
T2a	5 (19.2)
Missing	4 (15.4)
Pre-biopsy PSA (ng/mL): mean (SD)	7.3 (3.1)
TP biopsy: median [IQR]	
Total no. cores taken	28 [24–31]
Target no. cores taken	7 [6–8]
No. positive target cores	4 [3–6]
Template no. cores taken	18 [18–24]
No. positive template cores	2 [0–3]
Longest length cancer (mm)	7.5 [5–11]
ISUP grade-group	
1 (Gleason score 3+3)	1 (3.8)
2 (Gleason score 3+4)	25 (96.2)
PIRADS score	
3	1 (3.8)
4	19 (73.1)
5	5 (19.2)
Missing	1 (3.8)
Lesion location	
Base	7 (26.9)
Middle	9 (34.6)
Apex	9 (34.6)
Base to apex	1 (3.8)

IQR, interquartile range; PIRADS, prostate imaging-reporting and data system; PSA, prostate-specific antigen; SD, standard deviation; TP, transperineal.

Focal LDR brachytherapy consisted of a single monotherapy implant delivering a prescribed dose of 145 Gy to the F-PTV. Treatment was performed by an experienced brachytherapist. Iodine-125 Amersham brachytherapy seeds (model 6711) in a range of activities from (0.311mCi–0.500mCi) were utilised. Implantation was performed under general anaesthetic with patients in extended lithotomy position. Seeds were placed as per the pre-plan set-up under ultrasound guidance. A minimum distance of 3mm was maintained between seeds and the urethra, which was demarcated with an aerated gel. Intra-operative real-time dosimetric analysis was conducted within the VariSeed suite. Additional 'zulu' (free) seeds, were inserted if any clinically meaningful deviation from the intended plan was suspected. A non-contrast pelvic CT scan, co-registered with a same day mpMRI scan, was obtained 30 days post-implant in order to assess dosimetric outcomes. Follow-up occurred 4–6 weeks after seed implant and

then at three- to six-monthly intervals thereafter. Reviews included a clinical exam, prostate-specific antigen (PSA) test and toxicity assessment.

Outcome measures
To assess post-implantation dosimetry, the V100%, V150% and D90% for the F-GTV, V100% for the whole prostate, V200% for the urethra and V100% for the rectum were collected.

Baseline and post-treatment symptoms described in clinician notes were grouped under urinary, rectal and erectile domains and toxicity was assessed by retrospectively grading these according to the system used in the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0):

Grade 1 – mild; asymptomatic or mild symptoms; intervention not indicated
Grade 2 – moderate; minimal, local or non-invasive indication indicated
Grade 3 – severe or medically significant but not life threatening; hospitalisation indicated.

Oncological outcomes were assessed via serial PSA results and the findings of repeat mpMRI and TP biopsy which were performed 12–18 months post-treatment. The target region for the repeat TP biopsy was based on the lesion visible on the pre-treatment mpMRI.

Statistical Analysis
Analyses were performed in GraphPad Prism (v8.4.1). Numerical variables are presented as a median (interquartile range [IQR]) or mean (range), as specified. Frequencies are reported as a number and percentage of the assessable patients for a given outcome.

3.1.2.4 Results

Patient characteristics
Baseline patient characteristics are described in Table 2. All patients had unifocal disease on mpMRI, low to intermediate grade tumours (ISUP Grade Group 1 or 2) and a risk of nodal disease lower than 15% based on Kattan nomograms [313]. No patients received androgen deprivation therapy prior to, or at the time of, treatment. One patient was ineligible for mpMRI due to the presence of bilateral hip prostheses but had a targetable unifocal lesion on a ^{68}Ga-prostate specific membrane antigen positron emission tomography (^{68}Ga-PSMA-PET) scan.

Dosimetry

Intra- and post-operative dosimetry outcomes are summarised in Table 3. The mean (range) operating time for the seed insertion procedure was 36 minutes (23–47 minutes). The majority of men 24 (92.3%) were discharged on the day of treatment, with the remainder staying overnight for social reasons. All men passed their trial of void prior to discharge.

The mean (range) post-implantation V100% (Fig. 1a) and D90% (Fig. 1b) for the F-GTV were 92.3% (24.2–100) and 237.6 Gy (50.0–541.4), respectively. Twelve patients had a F-GTV V100% = 100% and 18 patients had V100% ≥98%. The first three consecutive patients had a F-GTV V100% <85%, prompting a change in planning technique from traditional seed placement to end-to-end seed clustering.

Twenty men (76.9%) had a rectal V100% (volume receiving 100% of the prescription dose) of zero, with the remaining six men having rectal $V_{100} < 1$ cc (12). The average (range) maximum urethral dose was 164.6 Gy (66.8–259.6) and 23 men (88.5%) had an unrecordable V200%. The mean (range) PTV size as a percentage of the prostate volume (PTV/prostate) was 24.5% (6.9–52.5) and the prostate V100% was 31.7% (9.2–62.2).

Table 3 Intra-operative and post-operative dosimetry outcomes

Variable	Value
Intra-operative	
Number of needles: median [IQR]	13 [11–15]
Number of seeds: median [IQR]	39 [34–47]
Total implanted activity (mCi)	16.7 [5.2]
Geometry, mean (range)	
Prostate volume (cc)	47.0 (19.3)
F-GTV (cc)	3.8 (4.4)
F-PTV (cc)	10.8 (6.0)
F-PTV (% of prostate volume)	24.5 (11.0)
F-GTV, mean (range)	
V100% (%)	93.2 (24.2–100)
V150% (%)	82.9 (9.8–100)
D90% (Gy)	237.6 (50.0–541.4)
Prostate, mean (range)	
V100% (%)	31.7 (9.2–62.2)
Urethra, mean (range)	
Max (Gy)	164.6 (66.8–259.6)
V200% (cc)	0.0 (0.0–0.01)
Rectum, mean (range)	
Max (Gy)	95.8 (18.4–278.1)
V100% (cc)	0.05 (0.00–0.84)

D90%, dose to 90% of the structure volume; F-GTV, focal gross tumour volume; F-PTV, focal planning target volume; IQR, interquartile range; SD, standard deviation; V100%, volume receiving 100% of the prescribed dose; V150%, volume receiving 150% of the prescribed dose; V200%, volume receiving 200% of the prescribed dose.

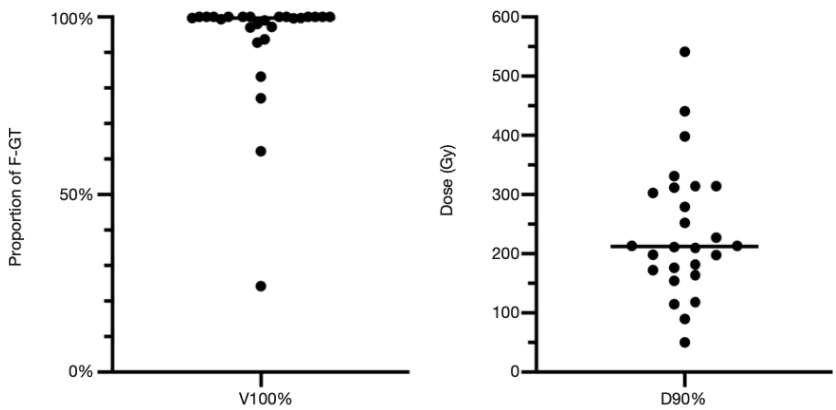

Figure 1 Post-implantation target dosimetry. The volume of the F-GTV receiving 100% of the prescription dose (A) and the dose to 90% of the F-GTV (B). V100%, volume receiving 100% of the prescribed dose; D90%, dose to 90% of the structure volume; F-GTV, focal gross tumour volume.

Toxicity

The median time from treatment to last toxicity assessment was 19.0 (IQR 12.4–30.5) months. Two patients were reviewed by clinicians outside of our institution and were lost to toxicity follow-up.

One patient developed a urinary tract infection one week post-implant that was managed with oral antibiotics and one patient went into urinary retention one week following implant, requiring temporary catheterisation. There were no acute re-admissions following implantation. The frequency and severity of urinary symptoms peaked within three months of treatment, with 9 (37.5%) and 7 (29.2%) presenting with grade 1 and 2 urinary symptoms, respectively, which resolved predominantly to baseline levels by the time of last follow up (Fig. 2a). Six of 13 patients with a F-PTV/prostate proportion greater than 20% had a grade 2 urinary toxicity following treatment, compared to 1 of 11 patients where the F-PTV/prostate proportion was less than 20%.

Eleven (45.8%) men reported a reduction in erectile function at any point after treatment compared to baseline, with 8 (33.3%) men continuing to have worse erectile function at the time of last follow-up (Fig. 2b). No grade 3 erectile dysfunction, refractory to pharmacological intervention, was reported.

Rectal toxicity was minimal (Fig. 2c) with only four (16.7%) patients having minor (grade 1) rectal symptoms post-treatment. One patient had grade 1 rectal toxicity at the time of last follow up.

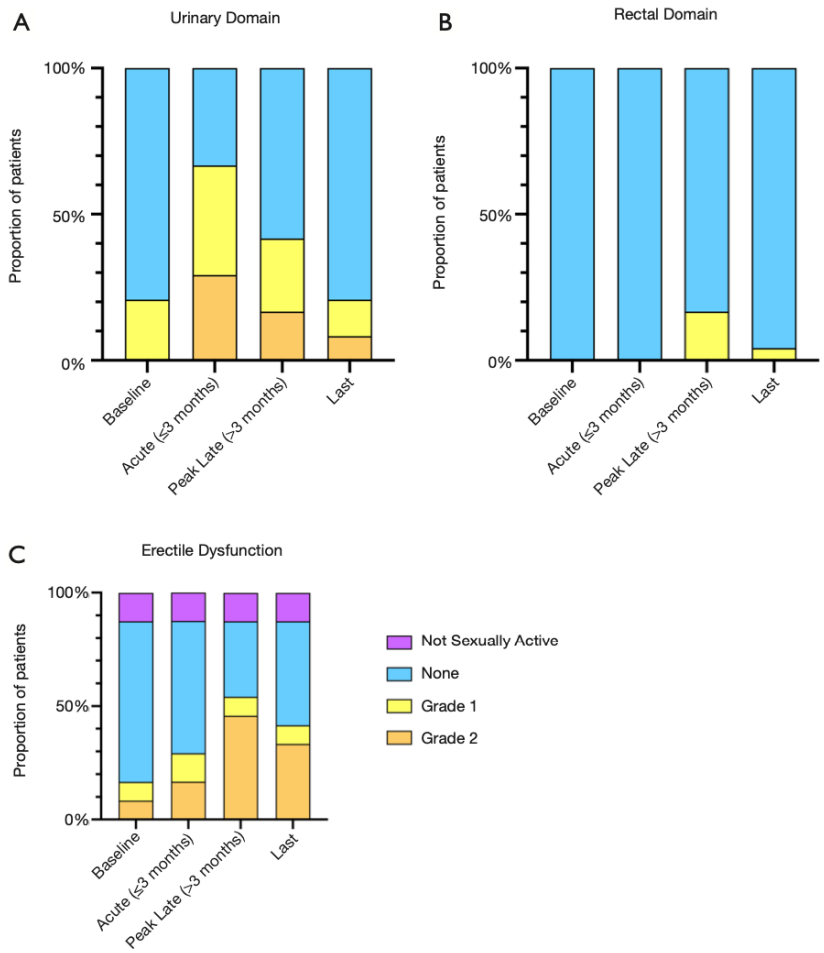

Figure 2 Summary of post-treatment toxicity over time. Rates of urinary (A) toxicity peaked acutely following treatment, before resolving mostly to baseline levels by the time of last follow-up. Rectal toxicity (B) was minimal at all time points, with no Grade 2 or higher toxicities reported. Rates of erectile dysfunction (C) peaked greater than 3 months post-treatment, with a resolution of symptoms in a minority of patients by the time of last follow-up.

Oncological outcomes

At the time of analysis, 12- to 18-month oncological outcomes were available for 21 patients via mpMRI and TP biopsy (n = 21) or mpMRI only (n = 1). The median time to repeat TP biopsy following treatment was 18.4 months (IQR: 12.9–19.3). No patients had clinically significant PCa, defined as ISUP Grade Group 2 or above. Histology results for the targeted index lesion/treatment area showed 7 men negative for malignancy with radiation effect present, 12 men with adenocarcinoma showing radiation treatment effect with no Gleason score assigned and 2 patients negative for malignancy with no neoplastic changes visible. Eighteen patients had no cancer detected in the remainder of the non-treated prostate and 3 patients had clinically insignificant disease (ISUP Grade-Group 1 with core length <10 mm). No lesion visible on repeat mpMRI had a PIRADS score ≥3. Eight patients returned a negative result while 10 patients had a lesion with a PIRADS score equal to 2.

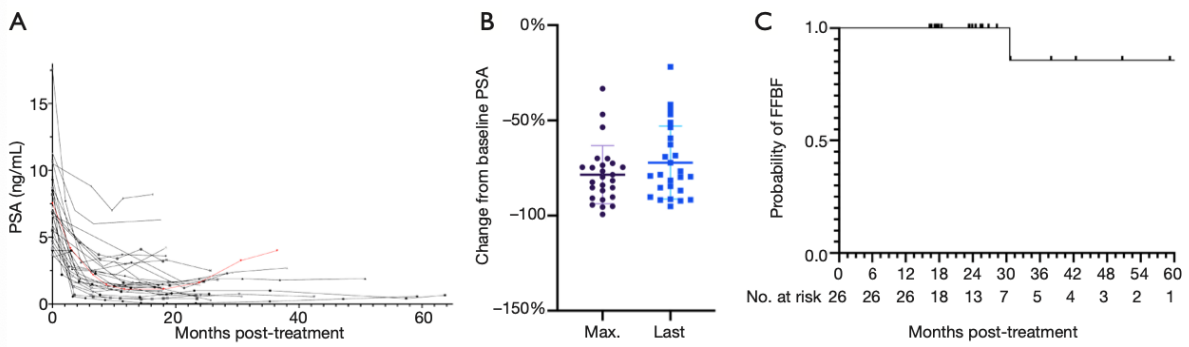

Figure 3 PSA outcomes following focal LDR brachytherapy. (A) PSA time-course for individual patients following treatment. (B) Maximum and last change in PSA from baseline. (C) Kaplan-Meier curve showing the probability of FFBF following treatment. PSA, prostate-specific antigen; LDR, low dose-rate; FFBF, free from biochemical failure.

The median PSA follow-up time for the cohort was 24.2 (IQR: 17.9–30.0) months (Fig. 3a). All patients had a reduction in PSA following focal LDR brachytherapy, with a mean decrease in PSA from baseline at last follow-up of 72.1% (range 21.9–95.1) (Fig. 3b). Of the 18 patients who had reached 18 months follow-up, all were free from biochemical failure (FFBF) (PSA >2 ng/mL above post-radiotherapy nadir [223]) (Fig. 3c). At 24 months, 13 out of 13 patients were FFBF. One patient, who had a F-GTV V100% of 97.0% and D90% of 163.6 Gy, and whose 12-month post-treatment biopsy had been negative, developed a rising PSA at 30 months and proceeded to an uncomplicated robotic-assisted radical prostatectomy. The final histopathology demonstrated an in-field recurrence of PCa (ISUP grade group 3) that was staged as T2N0M0 disease with clear margins.

3.1.2.5 Discussion

Advancements in modern imaging have facilitated a widespread move towards tissue-preserving strategies for cancer management, of which focal brachytherapy is an example for PCa. There are five prospective studies currently in recruitment across Europe, North America and Australia – including a clinical registry (Australian and New Zealand Trials Registry, CTRN12619001669189, LIBERATE) at our institution – investigating focal brachytherapy for selected PCa patients. This reflects an urgent need for further data to evaluate whether these techniques should be implemented more widely. While prospectively collected data continue to mature, the findings of this study affirm that lesion-targeted focal LDR brachytherapy is technically feasible, albeit with a learning curve, has a favourable toxicity profile compared to whole-gland treatments, and controls clinically significant cancer at 18–24 months following treatment.

Formal post-implant dosimetric evaluation criteria for focal LDR brachytherapy does not yet exist. Criteria for whole gland brachytherapy, such as the British Columbia Cancer Agency criteria [314], do not strictly require complete coverage of the prostate by the prescription dose, with a V100% >85% considered 'good' and ≥90% considered excellent. In contrast, in the focal setting, it is likely that near complete coverage of the focal GTV with the prescription dose will be critical. In a previous prospective trial of focal LDR brachytherapy, the criterion for a successful implant was a post-implant D100% ≥95% for the F-GTV [18]. This objective

was met in 16 of 17 patients, however, the mean focal GTV size was only 0.7 cc, compared to 3.8 cc in our study. A planning objective of V100% ≥98% to the focal volume has also been used previously [283,284]. The post-implant dosimetry and size of the focal target volume reported in our study is comparable to that reported by Cosset et al. [281], Mahdavi et al. [283] and Kunogi et al. [284] (Table 1).

The proportion of the prostate irradiated decreases progressively from whole-gland treatment to hemi-gland and lesion-targeted focal treatment of prostate cancer, and with this, the rate of toxicity is also expected to decrease. On average, the PTV was one quarter of the prostate volume in our study. Rates of grade 2 or higher acute and late urinary toxicity following whole-prostate LDR brachytherapy are reported to be up to 45% and 30%, respectively, including grade 3 or higher urinary toxicity in 5–10% of patients [296,315]. Using a grading system aligned with the CTCAE, 29% and 17% of men in our study had grade 2 acute and late urinary toxicity, respectively, with no grade 3 toxicities reported. Other studies of focal LDR brachytherapy report the majority of urinary toxicity within the initial six months following treatment, mostly resolving to baseline by 12 months [281,282]. Our results support this trend, with the initial worsening of urinary symptoms likely to reflect an inflammatory response from seed insertion.

Predictors of toxicity following whole-gland LDR brachytherapy include the number of needles used during insertion and the prostate V150% [315], and for focal treatment, lesions located at the base of the prostate [282]. While our study was not powered to detect predictors of toxicity, there did not appear to be a relationship between needle number or lesion location and urinary toxicity. However, a PTV/prostate proportion greater than 20% was associated with more grade 2 urinary toxicity. In a prospective study of 17 patients treated with focal LDR brachytherapy, Graff et al. [18] report only one CTCAE-defined grade 2 acute urinary toxicity and no late grade 2 toxicity, which is likely explained by the substantially smaller average F-GTV size (0.7 cm^3 versus 3.8 cm^3 in the present study) and a smaller proportion of the prostate being irradiated with the prescription dose. Taking these observations together, the F-PTV (or F-GTV) size as a proportion of the total prostate volume might be an important metric predictive of toxicity in the focal setting.

Similar to this study, the rectal dose (V100%) and subsequent toxicity associated with focal LDR brachytherapy has been universally reported as low to negligible [18,281,283]. In comparison, rates of grade 2 gastrointestinal toxicity have been reported to range from 1–19% following whole-gland LDR brachytherapy, with severe (grade ≥3) injuries including fistula reported in 1–2% of patients [289,316,317]. The insertion of a rectal spacer between the prostate and anterior rectal wall, which was performed for the 18 men with posterior lesions in this study, is likely to further decrease the likelihood of rectal symptoms following focal treatment.

The rate of erectile dysfunction requiring pharmacological or mechanical intervention following whole-gland LDR brachytherapy is reported to be at least 50% [303]**.** Initial data for focal brachytherapy suggest that erectile function returns to baseline levels for a substantial proportion of men after an initial decline in erectile function following treatment, however there is significant heterogeneity in the outcome measures used [18,281]. In comparison, we

observed an increase in the rate of erectile dysfunction requiring pharmacological intervention at the time of last follow up compared to baseline. However, our study could not distinguish between men receiving prophylactic intervention to maintain erectile function versus those being actively treated for a decline in function, making the true rate of erectile dysfunction likely to be lower than reported. The LIBERATE registry will prospectively collect these data as well as changes in international index of erectile function (IIEF) scores over time.

The oncological outcomes in this study are promising, however, longer term follow-up is required to assess the true efficacy of lesion-targeted focal treatment. A proportion of patients will experience recurrence despite initial disease control, as did one patient in our cohort who was negative for clinically significant disease at 12 months post-treatment.

Consensus guidelines from an international multidisciplinary group recently stated that the primary objective of focal therapy clinical trials for prostate cancer should be to demonstrate the focal ablation of clinically significant disease with negative biopsies at 12 months after treatment [318]. However, it is important to acknowledge that radiotherapy, histologic changes are not usually seen within 12 months of radiotherapy and complete histologic elimination of the tumour can take up to 3 years [319]. Furthermore, the interpretation of prostate histology following irradiation can be difficult due to radiation-induced cytoplasmic changes in benign tissue [320]. Repeat biopsies were performed at a median of 18.4 months (IQR: 12.9–19.3) post-treatment in the majority of the patients in this study, in alignment with active surveillance guidelines for PCa [321]. Consistent with our study, previous studies of focal LDR brachytherapy report repeat TP biopsy results at 12 months (Graff et al. [18], n=17 patients with all being negative), up to 18-24 months (Cosset et al. [281], n=6 patients with n=5 being negative). Madhavi et al. [283] report 24-month repeat TP biopsy results for two patients, finding no clinically significant cancer and demonstrating radiation effects in the respective focal target regions.

For patients treated with whole-gland external beam radiotherapy, patients with adenocarcinoma showing severe treatment effects at 2 to 3 years post-treatment have long-term disease-free survival equivalent to patients with a negative biopsy [322,323]. Further data on the relationship between histological and clinical outcomes following brachytherapy, and in particular, focal brachytherapy, are still required. The prospective LIBERATE registry, currently underway, will assess 18-month local control, based on repeat biopsy and mpMRI, alongside 5-year biochemical progression free survival. The applicability of standard definitions of biochemical failure following whole-gland radiotherapy [223] in the focal setting may not be valid and should also be investigated.

A potential disadvantage of focal therapy is that it may increase the toxicity and rate of complications associated with future salvage therapy, if it is required [27]. There is only weak evidence to date to suggest that the rate of complications, as well as functional and oncological outcomes, are acceptable post-salvage following primary focal therapy [324]. A better understanding of post-salvage treatment toxicity and oncological outcomes is a prerequisite for more widespread clinical use of focal LDR brachytherapy.

This study has several limitations. It is retrospective in nature and relatively small, lacking the power to formally interrogate predictors of toxicity following treatment at specific timepoints. Also, rates of toxicities were reported broadly under urinary and rectal domains, as it was not possible to identify specific toxicities in the medical records of all patients. Finally, many patients had a relatively short follow-up time, limiting conclusions about long-term toxicity and oncological outcomes.

3.1.2.6 Conclusion

This retrospective study contributes important data to the growing field of focal brachytherapy for PCa, which currently requires substantially more evidence to support widespread clinical implementation. We have demonstrated that focal LDR brachytherapy is safe and feasible, with encouraging preliminary oncological and functional outcomes. Prospective studies, such as the LIBERATE clinical registry at our institution, will answer crucial questions about the efficacy and utility of focal LDR brachytherapy, including quality of life outcomes measured by validated instruments, the impact on salvage therapy, and the correlation between repeat-biopsy and long-term biochemical control outcomes.

3.1.3 Commentary

Although this retrospective study only describes the outcomes of 26 patients, there is relatively little published on this subject in the literature. While duly acknowledging the limitations of this manuscript, we believe the data presented still makes an important contribution to the limited Focal LDR brachytherapy literature. In particular, we sought to address in our discussion a number of the current criticisms levelled at focal LDR brachytherapy, namely the lack of a formal dosimetric assessment criterion for focal LDR brachytherapy and the ideal timing for repeat histologic assessment of the prostate. Hopefully our summations will provide further validation for this technique so that it can be more widely adopted. Furthermore, this study has served as the genesis for the prospective registry for Focal LDR brachytherapy (LIBERATE), which is currently recruiting (see 3.3 Project 3).

3.2 Project 2

3.2.1 Introduction

The following manuscript forms Project 2. For further information regarding dosimetry outcomes, please see Appendix A: Focal LDR Brachytherapy Technique Protocol. The subject of this case report has signed a consent to publication form and the form is held by the treating institution.

At the time of thesis submission, this manuscript remains in the pre-submission phase.

3.2.2 Manuscript

Salvage Robotic Radical Prostatectomy Following Primary LDR Focal Brachytherapy For Prostate Cancer.

Elliot Anderson[1], Lloyd M. L. Smyth[2], Richard O'Sullivan[3,4], Andrew Ryan[5], Nathan Lawrentschuk[6,7,8,9], Jeremy Grummet[1,10], Andrew W. See[2]

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3.2.2.1 Introduction:

Definitive treatment for localized prostate cancer is associated with significant morbidity. Focal therapy for patients with low-intermediate risk features is an emerging modality aimed at reducing treatment-related toxicity. With the development of accurate diagnostic imaging using MRI, focal treatment with low dose rate (LDR) brachytherapy has become a viable ablation option. For this treatment modality to be validated, it is important to demonstrate that potential secondary or salvage treatment options are still practicable without impairment from the primary focal therapy. We describe a 67-year-old-male who underwent an uncomplicated salvage robot-assisted radical prostatectomy (S-RARP) following biochemical and histological failure at 36 months post focal LDR brachytherapy.

3.2.2.2 Case Presentation:

This 67-year-old-man had no significant past medical history. He initially presented with a PSA of 7.5 ng/ml and a PI-RADS 3 lesion in the right anterior transition zone on multiparametric-magnetic resonance imaging (mpMRI) (Figure 1). Transperineal prostate (TP) biopsy histology showed a congruent focus of Gleason 3+4 (ISUP Grade Group 2) with no other cancer. He was deemed suitable for focal LDR brachytherapy and received 14 needles/33

seeds for a planned target volume (PTV) of 8.4cc and prostate volume of 24.7cc. Postoperative dosimetry showed D90% 163.6 (Gy) and V100 97% (Figure 2). Following an uncomplicated recovery, his PSA fell appropriately reaching a nadir of 1.1 ng/ml at 18 months. His 12-month mpMRI was negative and repeat TP biopsy histology showed adenocarcinoma with radiation effect, no Gleason score assigned. At 36 months his PSA rose to 3.15 ng/ml, he was re-imaged with mpMRI showing a PI-RADS 4 lesion at the target area and he also underwent a gallium prostate specific membrane antigen (*PSMA*) ligand positron emission tomography (*PET*) scan that revealed a small PSMA ligand avid focus within the prostate gland matching with the mpMRI findings and no PSMA avid metastatic disease. A biopsy of that area showed a 3mm focus of Gleason score 4+3 (ISUP Grade Group 3). He proceeded to S-RARP with no reported increase in the difficulty of the operation, notably virgin surgical planes were identified and easily accessed at the prostate capsule overlying the focal treatment area. Histopathology showed clear margins and pT2 disease with the volumetric study demonstrating a lesion consistent with biopsy and imaging (Figure 3). Eighteen months post-RARP, the patient's PSA was undetectable with no postoperative complications. He currently requires one pad/day for minor urinary incontinence and he describes achieving 70% rigidity of pre-treatment erections, enabling intercourse with tadalafil.

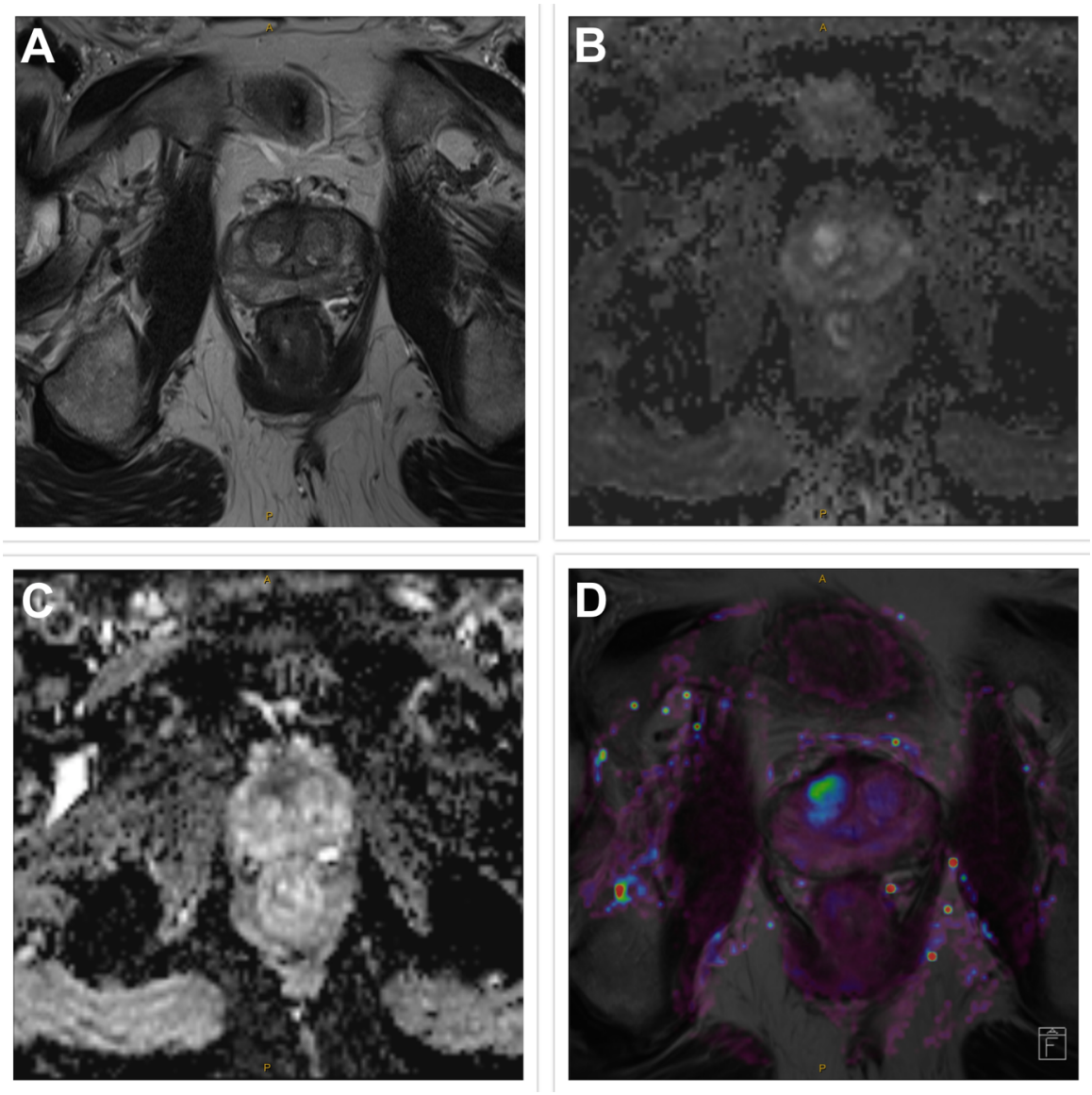


Figure 1: MpMRI demonstrating PI-RADS 3 Lesion
Lesion located in the anterior transition zone of the right mid prostate extending toward the apex. A) T2 weighted imaging showing an irregular 1.3cm area of decreased signal intensity B) increased signal intensity on high B value diffusion weighted imaging. C) Lesion showing restricted diffusion (ADC is 650). D) Lesion showing positive score on dynamic contrast enhancement.

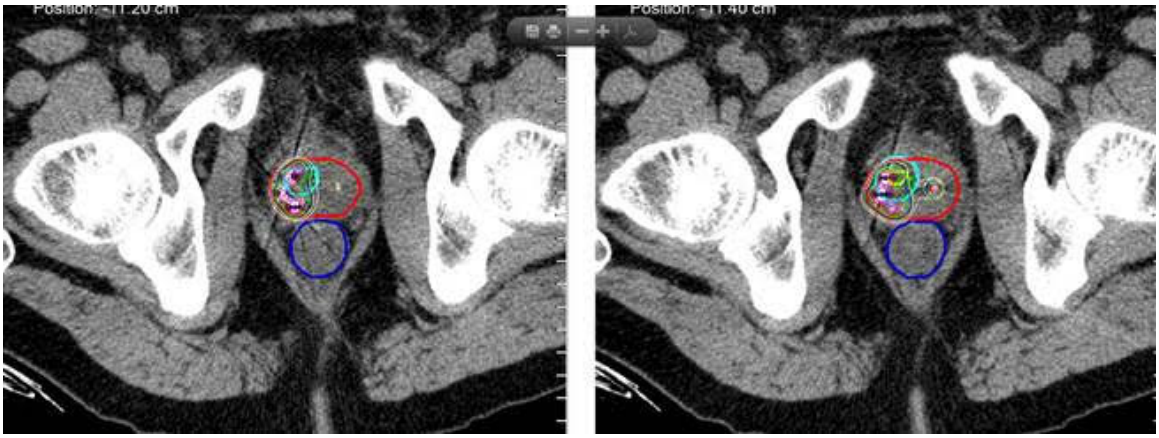
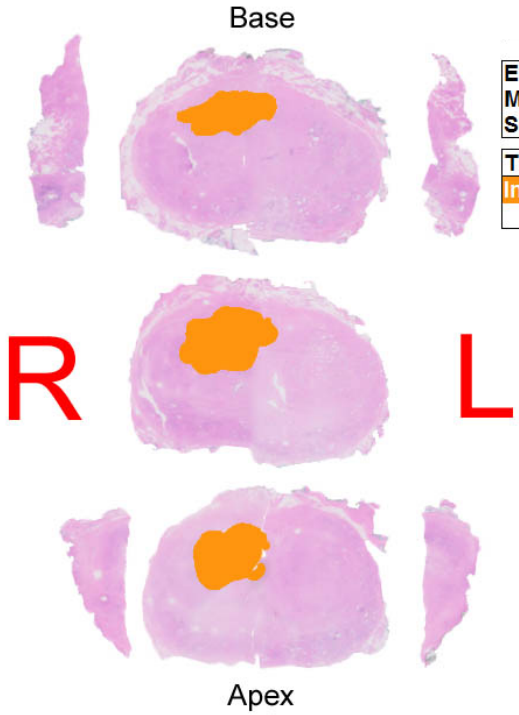


Figure 2: Intraoperative dosimetry schematic
Focal LDR brachytherapy dose plans demonstrating concentric radiation dosages outwards from targeted lesion, A) Preimplant B) Postimplant. The patient received 14 needles/33 seeds for a planned PTV of 8.4cc and prostate volume of 24.7cc. Postoperative dosimetry showed D90% 163.6 (Gy) and V100 97%.



Extra Prostatic Extension	Absent
Margins	Negative
Seminal Vesicle Involvement	Absent

TUMOUR VOLUME	
Index Tumour	1.3 cc
TOTAL	1.3 cc

Tumour volume	1.3 cc
Prostate volume	30 cc
% prostate involved	4.27%

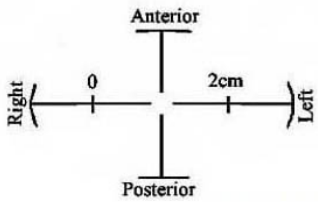


Figure 3: Radical Prostatectomy Histopathology Schematic
Histopathology of identified lesion showed clear margins and pT2 disease, volumetrically the lesion is congruent with the focally targeted index lesion.

3.2.2.3 Discussion:

Modern imaging improvements have facilitated a widespread move towards tissue-preserving strategies managing cancer. Focal therapy of the prostate is a hybrid approach which involves ablative treatment of the involved prostate gland and continued active surveillance of the unaffected gland [11]. The European Association of Urology (EAU) position paper on focal therapy (2018) sets out certain criteria that need to be satisfied before primary focal therapy can become an accepted treatment modality, including *"potential secondary or salvage treatment is not impaired by the primary focal therapy"* [27]. Historically, men who underwent salvage radical prostatectomy following previous radiotherapy were at risk of significant morbidity, with 50% of men reported to suffer a major complication [325]. This was due to greater tissue frailty and fibrosis that occurs following radiotherapy and increase in the difficulty of the operation. Since the advent of the robotic-assisted technique, morbidity following S-RARP has decreased, with complications requiring intervention reported in 16% of men [326].

An in-field recurrence following focal therapy, as described in this case, raises questions about oncological effectiveness and treatment efficacy. Intuitively, focal therapy success can be defined as the destruction of the targeted prostate lesion with preservation of non-cancerous native prostate tissue. What this means in terms of oncological outcomes is not well defined but retreatment rates of up to 20% following focal therapy have been deemed clinically acceptable by an expert consensus panel [200]. Given this expectation, surveillance post treatment becomes paramount as defined by the European Association of Urology (EAU) position paper on focal *therapy "reliable follow-up of the remaining prostate tissue"* [27]. This case report demonstrates the importance of regular PSA testing, repeat mpMRI and surveillance prostate biopsies so that any recurrence is detected as early as possible. Assessing the efficacity of LDR brachytherapy implants is difficult as no formal dosimetric assessment criteria specifically for focal LDR brachytherapy exists. Within the literature, the D90% and V100% are routinely reported by previous studies of Focal LDR brachytherapy [281,283,284] including a clinical trial of hemi-gland LDR brachytherapy report dosimetry outcomes based on the V100% and D90% [327]. Based on these reporting variables, this patient who had a F-GTV V100% of 97.0% and D90% of 163.6 Gy, received appropriately dosed implant to the target lesion. As such, this type of treatment failure following focal therapy should be considered an expected outcome in a minority of cases and patients should be counselled about the need for rigorous follow up and potential re-treatment.

Focal LDR brachytherapy aims to achieve similar oncological outcomes while limiting the post treatment genitourinary dysfunction by preserving non-cancerous prostate tissue, sparing the neurovascular bundles, bladder neck and urethra. Ribeiro et al demonstrated that salvage radical prostatectomy following focal therapy was associated with a significantly lower 30-day Clavien-Dindo I-IV complication rate compared to salvage radical prostatectomy following radiotherapy (5% vs 34%, $p<0.001$) [328]. Similarly, Marconi et al showed in the largest series of salvage surgery following focal therapy that S-RARP is safe with no increase in toxicity when compared to primary RARP [329]. However, in both studies the focal therapy arm did not involve patients who had undergone focal LDR brachytherapy, rather only patients who had

undergone HIFU, cryotherapy, electroporation, photodynamic therapy or topsalysin PRX302 as their primary therapy type were included.

To our knowledge, this is the first report of S-RARP following focal LDR brachytherapy. We did not encounter fibrosis or scarring secondary to radiation effect or note any distorted anatomy. The surgical planes were preserved and the surgeon's technique did not need to be modified. Our experience should be interpreted within the context of a favourable anterior lesion that was anatomically distinct from the rectum and neurovascular bundles and did not necessitate the use of a SpaceOAR hydrogel implant. We cannot comment on the difficulty of S-RARP for posterior lesions and what impact a rectal tissue spacer would have on salvage operations if utilised at the time of primary treatment.

3.2.2.4 Conclusion:

This proof-of-concept study shows that S-RARP following focal LDR brachytherapy is a safe procedure with no increase in technical difficulty. Although patient selection and careful implementation of surgical principles are of utmost importance.

3.2.3 Commentary

As outlined in the manuscript above, a key therapy component needed to validate focal LDR brachytherapy as primary treatment for carefully selected men with prostate cancer is the demonstration that subsequent salvage interventions are still possible. To date there has been no published description of a radical prostatectomy following focal LDR brachytherapy. This case report provides a proof of concept and also acts as an informative template for clinicians who encounter treatment failure following focal LDR brachytherapy. Radical prostatectomy should be considered a viable salvage option without consternation relating to previous radiotherapy treatment.

3.3 Project 3

3.3.1 Introduction

The following study forms Project 3.

Clinical registries are utilised to accurately and systematically record clinical data for quality improvement and research purposes and are widely used in the field of urology [330,331]. For example, Gullaumier et al, , recently published five-year efficacy and toxicity outcomes of a large, multi-centre prospective registry of men receiving focal therapy to the prostate via high-intensity focused ultrasound [332]. Our clinical research registry of men with low to intermediate risk prostate cancer treated with focal LDR brachytherapy aimed to achieve the following primary and secondary objectives:

Primary Objective

The primary objectives of this study were to determine:

- The rate of 18-month local disease control, and
- The rate of 5-year biochemical progression-free survival following focal LDR brachytherapy in men with low to intermediate risk PCa.

Secondary Objective

The secondary objectives of this registry were to:

- Determine the toxicity profile of focal LDR brachytherapy.
    - Particularly in the domains of urinary, gastro-intestinal and sexual function.
- Measure the change in patient-reported generic and disease-specific quality of life.
- Determine the rate of 3-year biochemical progression-free survival.
- Determine the rate of salvage treatment.
- Determine the rate of complications following salvage treatment.
- Determine the rate of biochemical failure after salvage treatment.

This study was conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

This protocol was developed in combination with Dr Elliot Anderson (Candidate), Dr Andrew See (Principal Investigator), A/Prof Jeremy Grummet (Co-Principal Investigator), Ash Plank (Statistician), Mel Grand (Trial Manager) and Lloyd Smyth (Clinical Researcher).

The registry was sponsored by Icon Cancer Foundation, which assumes responsibility for the overall conduct of this registry study, as well as arranging insurance and indemnity.

3.3.2 Methods

3.3.2.1 Study Design

This is a prospective, single-institution but multi-centre clinical registry.

3.3.2.2 Number of Participants

A total of 100 patients drawn from the patient population presenting for management of low to intermediate risk prostate cancer are being enrolled into the registry. The participants must meet all of the eligibility criteria to be enrolled in this study, as defined in section 3.3.2.5 'Eligibility Criteria'. A justification for the planned sample size, which includes allowance for 10% attrition, can be found in the Statistical Considerations section 3.3.2.9 'Statistical Methods'.

3.3.2.3 Primary Outcome Measures

Local Disease Control

Type of evaluation: Pathological.

Definition: The percentage of participants who reported negative or clinically insignificant disease in either treated or untreated prostatic tissue following repeat mpMRI fusion template prostate mapping (TPM) biopsy following focal Iodine-125 low-dose rate brachytherapy. Multi-parametric MRI fusion TPM biopsy is standard of care for men following focal LDR brachytherapy for PCa.

Method of measurement: Tissue samples collected from transperineal TPM biopsies were processed at a suitable pathological practice and undergo independent review by qualified pathologists.

Definition of response:

Pathological control will be declared if all cores examined demonstrate either, or both, of the following:

- No visible neoplastic characteristics (negative disease); and
- ≤ Gleason 6 (3+3) in <10mm of core (clinically insignificant disease);

Pathological progression will be declared if any of the following criteria are met:

- No pathological changes from baseline (stable disease);
- Maximal core length of Gleason 6 increases from baseline biopsy; or
- Tumour upgrading (increase in percentage high grade tumour or increased Gleason score) compared to baseline

Frequency of assessment: This endpoint will be assessed at 18 months after LDR brachytherapy seed implantation, or upon biochemical progression, whichever is

earlier. Multi-parametric MRI fusion template prostate mapping (TPM) biopsy at this timepoint is standard following focal LDR brachytherapy for PCa.

Classification: Treatment failure is classified as in-field or out-of-field depending on whether or not biopsy-proven recurrent or progressive disease is confined within the treated PTV.

Biochemical Progression-free Survival

Type of evaluation: Biochemical.

Definition: The time from patient enrolment to the date of biochemical progression – defined as an increase in PSA by greater than or equal to 2 ng/mL above the nadir in which the PSA velocity following the nadir was greater than 0.75 ng/ml per year [333].

Method of measurement: Blood samples were collected and processed at the pathology laboratory that performed baseline PSA evaluation according to the department's protocols.

Frequency of assessment: Serum PSA was collected and analysed prior to all routine follow-up appointments following treatment. The appointments were at 6 weeks following treatment, then three-monthly for 24 months following treatment, then six-monthly until five years following treatment, or upon withdrawal or pathological or biochemical failure. Serum PSA testing at this frequency is standard of care for men following treatment for PCa.

Classification: PSA velocity (PSAvel) was calculated in ng/mL/year from the slope of the least-squares regression line determined from the raw data. This was calculated using an appropriate tool or web resource such as https://www.mskcc.org/nomograms/prostate/psa-doubling-time.

3.3.2.4 Secondary Outcome Measures

Toxicity Evaluation Criteria

Type of evaluation: Physician assessment (unblinded).

Definition: Treatment-related toxicity was defined as any deleterious effect which may have occurred as a result of focal LDR brachytherapy. Events occurring within 90 days of LDR brachytherapy treatment were defined as '*acute*', and any adverse event occurring more than 90 days after seed implantation was defined as '*late*'. Adverse events were also reported chronologically based on the number of months post treatment. This registry utilised the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v5.0 to classify all adverse events.

Frequency of assessment: Toxicity was assessed at both patient enrolment (baseline) and every routine follow-up appointment (scheduled and unscheduled) until the final follow up appointment at five years or withdrawal from the study. Assessments were

at 6 weeks post-treatment, three-monthly for 24 months following treatment, then six-monthly until five years post-treatment. Clinical assessment at this frequency is standard of care for men following brachytherapy for PCa.

Classification: Treatment-related toxicities was categorised into grades from 0 to 5, with definitions as follows:

- Grade 0 - no adverse events,
- Grade 1 - mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated,
- Grade 2 - moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*,
- Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**,
- Grade 4 - life-threatening consequences or urgent intervention indicated, and
- Grade 5 - death related to adverse event.

(*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)

An abbreviated and full NCI Common Terminology Criteria for Adverse Events (version 5.0) reference guide can be located at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Patient-reported Quality of Life

Type of evaluation: Paper questionnaire, patient self-assessment.

Definition: change in patient-reported quality of life from baseline as measured by the following instruments:

a) SF-12® Short Form Health Survey (v1.0)[334];
b) International Prostate Symptom Score (IPSS)[335];
c) International Index of Erectile Function (IIEF-5)[336] (v2.0); and
d) Expanded Prostate Cancer Index Composite (EPIC)[337] Bowel Domain (v1.0).

Frequency of assessment: All questionnaires were completed by patients following written informed consent (baseline) and at pre-defined routine follow up appointments following focal LDR brachytherapy until the final follow up appointment at 60 months or withdrawal from the study.

Classification/Scoring:

a) SF-12 is a widely employed brief 12-item measure of generic or general health-related quality of life/health status that includes composite or summary scales reflecting perceived physical and psychosocial health and functioning. Individual responses are used to calculate a score for each of the two summary scales: Physical Component Summary (PCS) and the Mental Component Summary (MCS). The PCS and MCS are computed using the scores from the same 12 questions, but with different weights, and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health. The average PCS-12 and MCS-12 for the United States population are both 50 points, with one standard deviation being 10 points away from average.

b) The International Prostate Symptom Score (IPSS) is a validated questionnaire that will be used to score urinary toxicity (symptoms) before and after focal brachytherapy. Scores will be classified as following:

- Mild = 0 to 7;
- Moderate = 8 to 19;
- Severe = 20 to 35.
- The quality of life component of the IPSS questionnaire will also be used to score quality of life due to urinary symptoms that may arise after focal brachytherapy (0 to 2 = good; 3 to 4 = acceptable; 5 to 6 = poor).

c) The International Index of Erectile Function (IIEF-5) is a 5-item questionnaire that will be used to score erectile dysfunction (ED) after focal brachytherapy [338]. Scores will be classified as following:

- No ED = 22 to 25;
- Mild = 17 to 21;
- Mild to moderate = 12 to 16;
- Moderate = 8 to 11;
- Severe = 5 to 7.

d) Expanded Prostate Cancer Index (EPIC) bowel domain (version 1.0) will be used to evaluate changes in bowel toxicity following focal LDR brachytherapy. Response options for the EPIC bowel domain forms a Likert scale, which are then transformed linearly to a 0-100 scale, with higher scores representing better health-related quality of life (HRQoL).

Rate of local salvage therapy

Type of evaluation: Physician assessment

Definition: The percentage of patients who receive a subsequent local treatment as a result of biochemical progression and/or local disease progression following focal LDR brachytherapy. Local salvage therapy included, but was not limited to the

following modalities: radical prostatectomy, external beam radiotherapy, brachytherapy, HIFU and cryoablation.

Classification: Presence of absence of local salvage therapy

Frequency of assessment: The presence of absence of local salvage therapy, including the type of salvage therapy delivered, will be recorded at each follow up visit up within the 60 months follow up period.

Rate of complications related to local salvage therapy

Type of evaluation: Physician assessment

Definition: The percentage of patients who experience a specific complication or complications during or following local salvage therapy.

Method of measurement:

1. The type of complication(s) was described by the physician(s) involved in performing the salvage therapy. For local salvage therapies involving surgery, the Clavien-Dindo classification system [339]for surgical complications was used to grade the complication(s)
2. Deviations from the standard delivery of the salvage therapy was recorded by the treating physician(s).

Frequency of assessment: Post-salvage therapy complications was assessed at each scheduled follow-up visit up within the 60 months follow up period, for applicable patients who receive a local salvage therapy. Additional unscheduled study follow-up visits were conducted at the discretion of the physician.

Rate of biochemical progression following salvage treatment

Type of evaluation: Biochemical.

Definition: The percentage of patients who progress biochemically following local salvage treatment. Biochemical progression in this setting was defined as an increase in PSA by greater than or equal to 2 ng/mL above the nadir following external beam radiotherapy, brachytherapy, HIFU or cryoablation, or an increase in PSA by greater than or equal to 0.2 ng/mL above the nadir (with a second subsequent confirmatory reading) following salvage radical prostatectomy.

Method of measurement: Blood samples will be collected and processed at the pathology laboratory that performed baseline PSA evaluation according to the department's protocols.

Frequency of assessment: Serum PSA was collected and analysed prior to all routine follow-up appointments following treatment, and the additional unscheduled study

visits following salvage treatment. The unscheduled visits will take place approximately 6 weeks following salvage treatment, then three-monthly for 24 months following salvage treatment, then six-monthly until reaching the 60-month registry follow-up period, or upon withdrawal. Serum PSA testing at this frequency is standard of care for men following treatment for PCa.

3.3.2.5 Eligibility Criteria

Participants in this research registry were recruited from the population of men receiving focal LDR brachytherapy for low to intermediate risk PCa as standard of care at the study sites.

Inclusion Criteria

Patients who met the following inclusion criteria were considered eligible for focal LDR brachytherapy as standard of care and subsequent enrolment into the LIBERATE registry:

- Men 40-85 years of age (inclusive);
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Life expectancy > 10 years based on co-morbidity not related to prostate cancer.
- Prostate specific antigen (PSA) level ≤ 15 ng/ml
- Prostate cancer clinical stage T1c or T2a
- PIRADS score of 3-5 (inclusive) or suspicious prostate lesion on PSMA-PET*
- Reproducible template biopsy of the prostate gland demonstrating:
    - Histologically-proven index lesion Gleason 6 (≥10mm in ≥1 core) or 7 (3+4) or 7 (4+3) (longest core <10mm) adenocarcinoma coinciding with mpMRI;
    - Template biopsies of the remaining gland, with minimum 18 cores taken
    - Non sector positive prostate containing no cancer or clinically insignificant cancer (cancer core length <10mm Gleason 3+3)
- No significant urinary obstructive symptoms.
- Able to participate in the stipulated follow-up (either telephone follow-up or on-site visits acceptable, but one follow-up annually should be in person).
- Patients or their legal representatives must have the ability to read, understand and provide written informed consent.

* PSMA-PET was used in this study as an alternative to MRI at baseline for diagnostic purposes. This may have been due to contraindications for MRI (due to claustrophobia, pacemaker, bilateral hip replacement etc.) and were utilised at the clinician's discretion. If PSMA-PET was used at baseline it was repeated at 18 months post-treatment.

Exclusion Criteria

Patients who meet any of the following criteria were not eligible for focal LDR brachytherapy or enrolment into the LIBERATE registry:

- Evidence or suspicion of extra-capsular extension on MRI.

- Prostate cancer with significant sarcomatoid, ductal, spindle cell or neuroendocrine small cell components.
- Any other active malignancy (untreated, progressive or recurrent), except for non-melanoma skin cancer.
- Any inactive malignancy diagnosed within 5 years of entry, except for non-melanoma skin cancer.
- Any anatomical abnormality or medical condition precluding brachytherapy planning or treatment, or follow-up imaging (i.e. unable to cease anti-coagulant therapy, contraindications to anaesthesia, imperforate anus, TURP defect, diffuse intra-prostatic calcification, unfavourable prostatic geometry etc.)
- Chronic or acute prostatitis, neurogenic bladder, urinary tract infection, sphincter abnormalities, or any other symptom that prevents normal micturition.
- Patients who have received, or are receiving, any form of localised or systemic treatment (including ADT) for prostate carcinoma (excluding 5α-reductase inhibitors).
- Patients who are unwilling or unable to adhere to study requirements, including treatment and required assessments.
- Patients opt-out of participating in the registry in writing (TBC depending on decision around Informed consent process below)

3.3.2.6 Study Protocol

Study participants were assessed as per the following study visits and procedures schedule (see below).

	Pre-Treatment	LDR	Follow up period^												
			Post-Implant	6 wks	3m	6m	9m	12m	15m	18m	21m	24m	6 monthly (30m-5yrs)	Unscheduled visits	Progression
mp-MRI (T1/2, DWI, DCE) (or PSMA PET)	✓									✓					✓
TPM biopsy	✓									✓					✓
Assess eligibility criteria	✓														
Review medical history	✓														
Review medications	✓														
Clinical assessment	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Informed consent	✓														
PSA assessment	✓#			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Volume study	✓														
Focal LDR brachytherapy		✓													
Post-implant CT/MRI*			✓												
Post-implant dosimetry			✓												
Acute toxicities (CTCAE)	✓			✓	✓										
Late toxicities (CTCAE)						✓	✓	✓	✓	✓	✓	✓	✓	✓	
SF-12v2**	✓			✓		✓		✓		✓		✓	✓		
IPSS**	✓			✓		✓		✓		✓		✓	✓		
IIEF-5**	✓			✓		✓		✓		✓		✓	✓		
EPIC bowel domain**	✓			✓		✓		✓		✓		✓	✓		

All scheduled follow up appointments will be held within 2 weeks (for 6 week and 3 month appointments) or a month (all other appointments) of the ideal visit date. All visits and procedures are Standard of care with the exception of the registry specific questionnaires.
Patients on finasteride (duodart) must cease following Volume Study and have PSA rechecked
*The timing of the post-implant CT and MRI is dependent on participant availability and machine availability and can occur anywhere from Day 1 to Day 35 (or even later if required)
** Questionnaires used are registry specific and not part of standard of care

3.3.2.7 Management of Progression

Biochemical Progression

Participants who met the criteria for biochemical progression underwent a repeat mpMRI and TPM biopsy to assess for pathological progression and were reviewed by the investigator. If the biopsy did not show pathological progression, the trial follow-up schedule was continued (with additional unscheduled visits and investigations as clinically indicated).

Pathological Progression

If a participant had pathological progression, they underwent one form of salvage treatment. Once they received the treatment, they continued to be reviewed by the investigator as per the trial follow-up schedule with additional unscheduled visits if required.

Metastatic Disease

If a participant was found to have metastatic disease, no further trial follow-ups were conducted. Local disease status was recorded at the time metastatic disease diagnosis then no further data was collected, and participants returned to normal clinical care.

3.3.2.8 Technique Protocol

Please refer to Appendix A: Focal LDR Brachytherapy Technique Protocol.

3.3.2.9 Statistical Methods

Sample Size Estimation

The primary endpoints consist of the proportion of patients exhibiting local control at 18-months and the proportion of patients achieving biochemical progression-free survival at 5 years following focal LDR brachytherapy, in a single patient group. Sample size calculations were based upon the expected precision, or margin for error, of point estimates for proportion of patients exhibiting local control at 18-months and biochemical progression-free survival at 5 years. Calculations were undertaken using Stata 14 (Stata Corporation, College Station, Texas, 2015).

Precision refers to the half-width of a 95% confidence interval (CI). A precision of 15% or 0.15, for example, would indicate that the 95% confidence interval for a proportion of 0.50 would be no wider than 0.35 to 0.65 (i.e. 0.50 plus or minus 0.15). Employing exact binomial 95% confidence intervals, a sample size of 45 patients would allow precision, or margin for error, of no wider than 0.16 for any proportion, and no wider than 0.15 for proportions of 0.80 or greater (e.g. 0.80 plus or minus 0.15). Based upon prior studies [231,333], the proportion of patients exhibiting local control and biochemical progression-free survival would be expected to at least 0.80 in each case. Exact binomial 95% confidence intervals for various proportions appear in the table below.

Obtained proportion	n out of 45	95% CI	Largest precision or margin for error (half-width of 95% CI)
0.62	28	0.47 to 0.76	0.16
0.71	32	0.56 to 0.84	0.15
0.80	36	0.65 to 0.90	0.15
0.89	40	0.76 to 0.96	0.13
0.98	44	0.88 to 1.00	0.10

Table 6: Study Sample Size Estimation
Histopathology of identified lesion showed clear margins and pT2 disease, volumetrically the lesion is congruent with the focally targeted index lesion.

Allowing for 10% attrition would require a total of 100 patients. The above sample size is thought to be feasible in that 2 patients would be typically recruited per month, requiring data to be collected over 60 months.

Statistical Analysis Plan

Descriptive statistics were reported using frequencies and percentages or proportions for binary or categorical data. Percentages were calculated based upon the number of patients for whom was available. Continuous or dimensional variables were summarised using means and standard deviations, with medians and interquartile ranges (difference between 25th and 75th percentiles) reported for potentially skewed data such as PSA or SF-12.

The primary endpoints of the proportion of patients exhibiting local control at 18 months (1) and the proportion of patients achieving biochemical progression-free survival at 5 years (2), could not be analysed at the time of the interim analysis undertaken for this theiss. At the completion of this study primary endpoint (1) will be analysed using proportions, and primary endpoint (2) will be assessed using a single-group Kaplan-Meier survival curve.

In regard to secondary endpoints, changes in variables such as SF-12v2 over time were assessed using methods appropriate for analysis of longitudinal data, such as mixed models / hierarchical linear modelling or generalised estimating equations (GEE) models appropriate to the scale of data being measured and the sample size. Appropriate graphs of changes over time and simple pairwise comparison between baseline and 6 weeks, then every 6 months up to 5 years or withdrawal were created, with maximum change being expected between baseline and 6 weeks following treatment. If missing or questionable data was identified, the study team investigated to clarify and seek restoration of missing observations. If unable to be identified from source the missing observations were reported for all endpoints. 95% confidence intervals are presented throughout, and any tests of statistical significance employ an alpha of 0.05, two-tailed. All analyses was conducted using standard professional statistical software, i.e., Stata (Stata Corporation, College Station, Texas).

3.2.3 Results

3.2.3.1 Patient Characteristics

At the time of the preliminary analysis undertaken for this thesis (22 months since LIBERATE registry opened) 43 patients had been enrolled. Baseline patient characteristics are described in Table 7. All patients met the eligibility criteria outlined in section '3.3.2.5 Eligibility Criteria'. Of note, two patients were ineligible based on mpMRI criteria but had a unifocal targetable lesion on a PSMA-PET scan.

Table 7. Patient characteristics (N =43)		
Characteristic		
Age: mean (SD)		68 (6.6)
Pre-biopsy PSA (ng/mL): mean (SD)		6.3 (2.3)
Pre-biopsy Free/Total PSA (ng/mL): mean (SD)		12.5 (4.9)
Template Biopsy no. cores: median [IQR]		
Total		30 [26 – 31]
Target		7 [6 – 8]
Template		20 [18 – 24]
Gleason score	3 + 4	37 (86%)
	4 + 3	6 (14%)
Multiparametric MRI		
Prostate volume (cc): mean (SD)		34 (12.1)
PIRADS score		
2		2 (5%)
3		3 (6%)
4		28 (65%)
5		10 (23%)
PSMA-PET Criteria		2
Lesion Location		
Base		6 (14%)
Middle		21 (49%)
Apex		16 (37%)
Abbreviations: IQR, interquartile range; PIRADS, prostate imaging-reporting and data system; PSA, prostate-specific antigen; SD, standard deviation.		

3.2.3.2 Dosimetry

Table 8 summarises the intra-and post-operative dosimetry outcomes for LIBERATE patients. The mean (range) post-implantation V100% and D90% for the F-GTV were 98.51% (89.26-

100%) and 244.13 Gy (143.11-450.33 Gy), respectively (Figure 10). Twelve patients had a F-GTV V100% =100% and 21 patients had V100% ≥98%.

Twenty-three (79%) men had a rectal V100% of zero, with the remaining five men having rectal V100% <0.5 cc. The average (range) maximum urethral dose was 143.38 Gy (39.88-285.01) and 24 (82%) patients had a V200% of zero. The mean PTV as a percentage of the prostate volume (PTV/prostate volume) was 20% and the prostate V100% was 22.3% (8.71-47.33%).

Table 8. Intra-operative and post-operative dosimetry outcomes (N=29)

Variable	*Value*
Intra-operative, Median [IQR]	
Number of needles:	9 [8 -10]
Number of seeds:	26 [23 – 32]
Total implanted activity (mCi)	10.25 [4.2]
Geometry, Mean (Range)	
Prostate volume (cc)	40.5 (16.6–86.1)
F-GTV (cc)	3.8 (0.6-4.3)
F-PTV (cc)	8.1 (2.5 – 26.51)
F-PTV (% of prostate volume)	20
F-GTV, Mean (IQR)	
V100% (%)	98.34 (97.76-100)
V150% (%)	89.85 (86.34– 96.98)
D90% (Gy)	245.37 (198.37-292.91)
Prostate, Mean (Range)	
V100% (%)	22.3 (8.71 – 47.33)
Urethra, Mean (Range)	
Max (Gy)	143.38 (39.88– 285.01)
V200% (cc)	0.03 (0.0 – 0.84)
Rectum, Mean (Range)	
Max (Gy)	48.14 (11.81 – 142.53)
V100% (cc)	0.02 (0.00 – 0.5)
SpaceOar (%)	22 (75)

Abbreviations: D90%, dose to 90% of the structure volume; F-GTV, focal gross tumour volume; F-PTV, focal planning target volume; IQR, interquartile range; SD, standard deviation; V100%, volume receiving 100% of the prescribed dose; V150%, volume receiving 150% of the prescribed dose; V200%, volume receiving 200% of the prescribed dose.

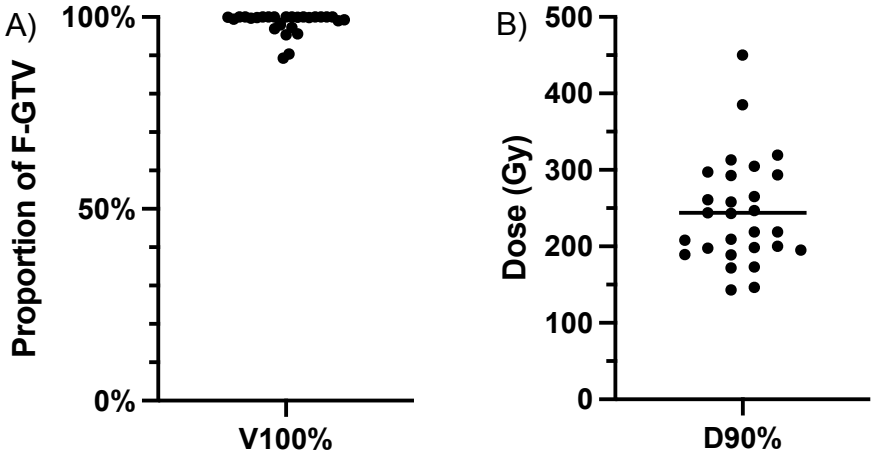


Figure 10: Post-implantation target dosimetry.
The volume of the F-GTV receiving 100% of the prescription dose (A) and the dose to 90% of the F-GTV (B). V100%, volume receiving 100% of the prescribed dose; D90%, dose to 90% of the structure volume; F-GTV, focal gross tumour volume.

3.2.3.3 Toxicity

The median time from treatment to latest CTCAE assessment is 9 (IQR 3-12) months (Figure 11). Within the urinary domain, the proportion of men reporting grade 1 adverse events peaked in the acute period following treatment then trended towards baseline at 12 months. Rectal toxicity was uncommon and mild, two patients reported grade 1 diarrhoea (<4 stools per day over baseline) and one patient reported grade 1 proctitis (rectal discomfort, intervention not indicated) at 12 months. The proportion of men reporting higher grade erectile dysfunction increased over time. At 6 months two patients reported grade 3 impairment defined as erectile dysfunction refractory to erectile aids. At the 12-month assessment this grade impairment persisted in one patient and had improved to grade 2 in the other. Of note the patient with ongoing grade 3 toxicity reported grade 2 toxicity at baseline and required the use of erectile aids pre-treatment.

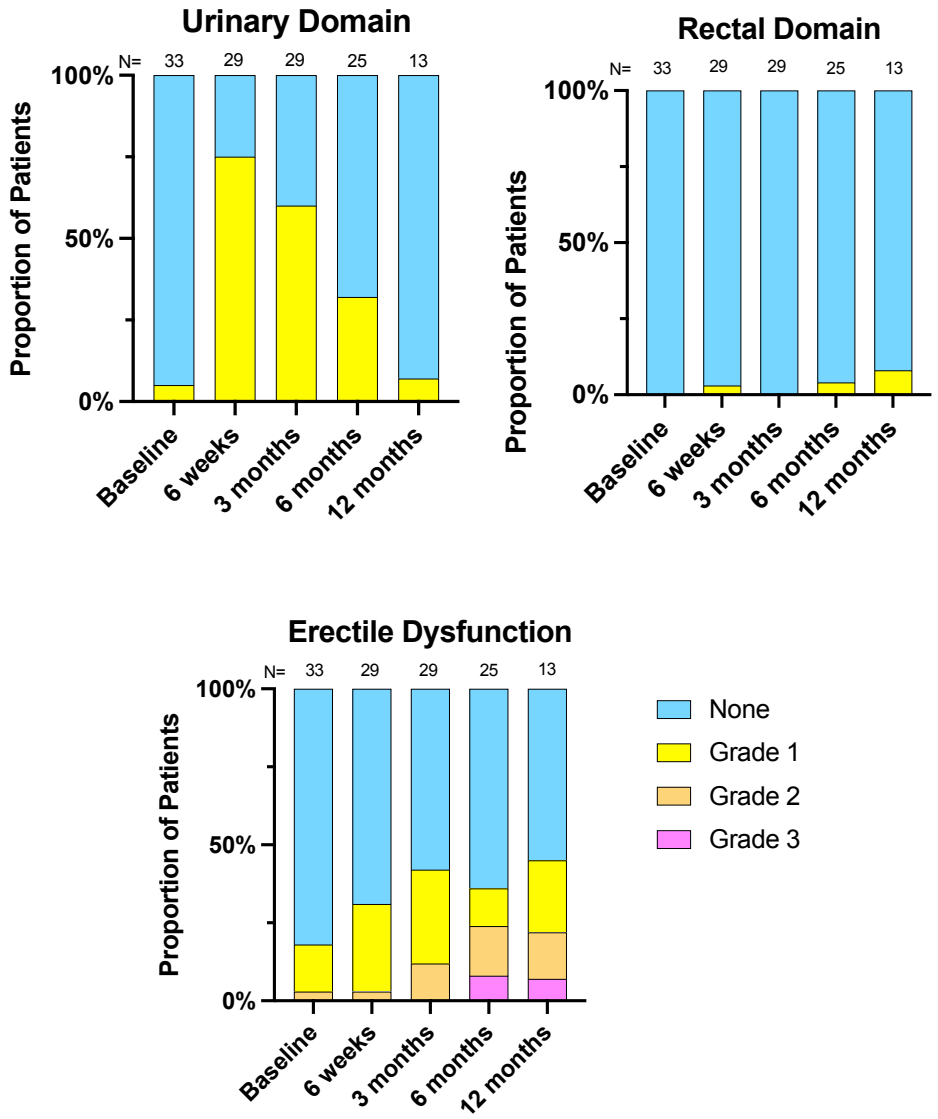


Figure 11: Summary of post-treatment toxicity categorised by CTCAE (V5).

The median time from baseline to latest SF-12 Short Form Health Survey was 4.5 (IQR 1.3-7.5) months. Over the course of the analysis, the average reported 'mental' health scores was greater than the standardised population score of 50. This was also the case with the 'physical' health score until 18 months, when the average score fell to 41 based upon questionnaire results from four patients (Figure 12).

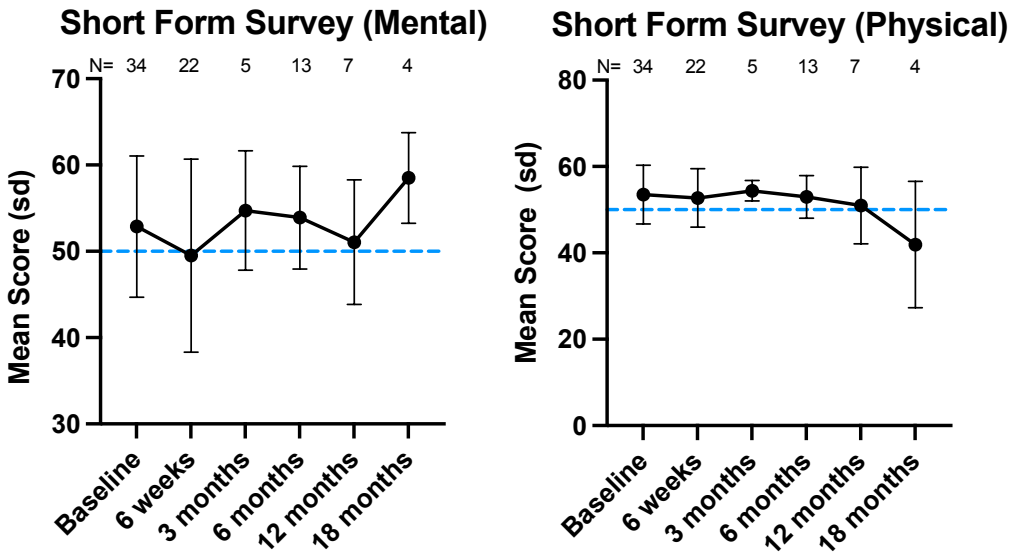


Figure 12: Short Form Health Survey (SF-12)
The blue line indicates the average score for the United States population, each increment of 10 points above or below 50, corresponds to one standard deviation away from the average.

Results from IPSS and IIEF-5 patient reported quality of life self-assessments are shown in Figure 13. The median time from baseline to last assessment was 6 (IQR 1.3-12) months and 4 (IQR 1.3-6) months respectively. The mean change in patient score from baseline to last follow up was 4 and -2.5 points for IPSS and IIEF-5 respectively. The minimal clinically important difference in IPSS score has been defined as a change of three point to the total IPSS score [340]. Based on the 12-month IPSS assessment, 5 (70%) men demonstrated no change, 1 (14%) man had a clinically meaningful improvement in his symptoms and 1 (14%) man had clinically meaningful impairment to his urinary function. Comparatively, the 6-month IPSS assessment showed 7 (54%) men with no change, 2 (15%) men with a clinically meaningful improvement to function and 4 (31%) men who had a clinically meaningful deterioration in function. Review of the IPSS quality-of-life component showed no change was reported in 14 (52%) patients, improvement in 7 (27%) patients and worse quality in 6 (21%) patients. The minimal clinically important difference in IIEF score can be assessed based on a change in total score (mild: 2; moderate 5; severe 7) [341]. At 12 months, 2 (50%) patients had no change to function, 1 (25%) patient had mild impairment and 1 (25%) patient had a severe decrease in function. At 6 months, 7 (54%) men reported no change, 1 (8%) man reported mild impairment, 2 (16%) had a moderate decrease and 1 (8%) man had severe decline. Interestingly two (16%) men reported clinically meaningful improvement in function. Across the whole cohort the average score in both instruments had returned to the baseline level at the 12-month review.

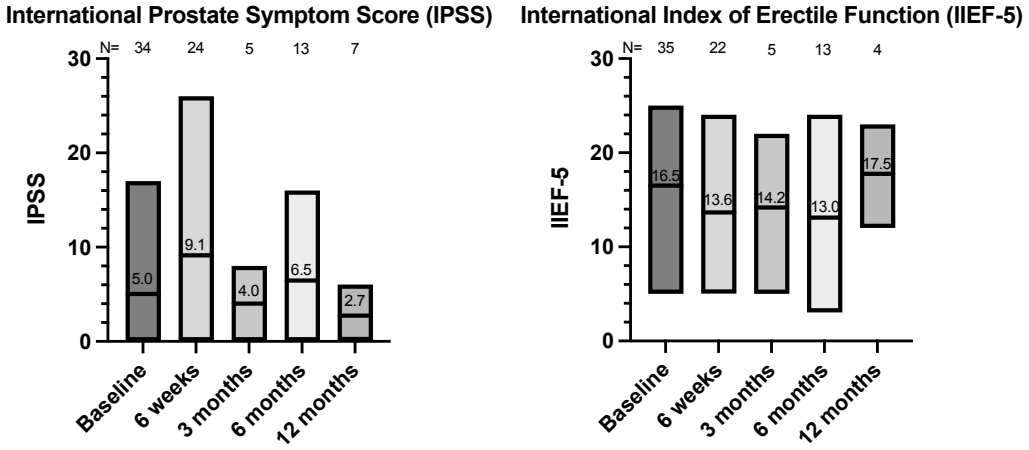


Figure 13: International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF-5). Floating bars showing min/max value with waist at mean result.

EPIC bowel domain scores are reported in Figure 14. The median time from baseline to last review was 4 (IQR 1.3-8) months. Clinically significant changes in scores were defined as ½ standard deviation above and below the baseline mean. Men reported better HRQoL in the 'Bother' subscale compared with the 'Function' component whose nadir score at 3 months represented a clinically significant change from baseline at this timepoint.

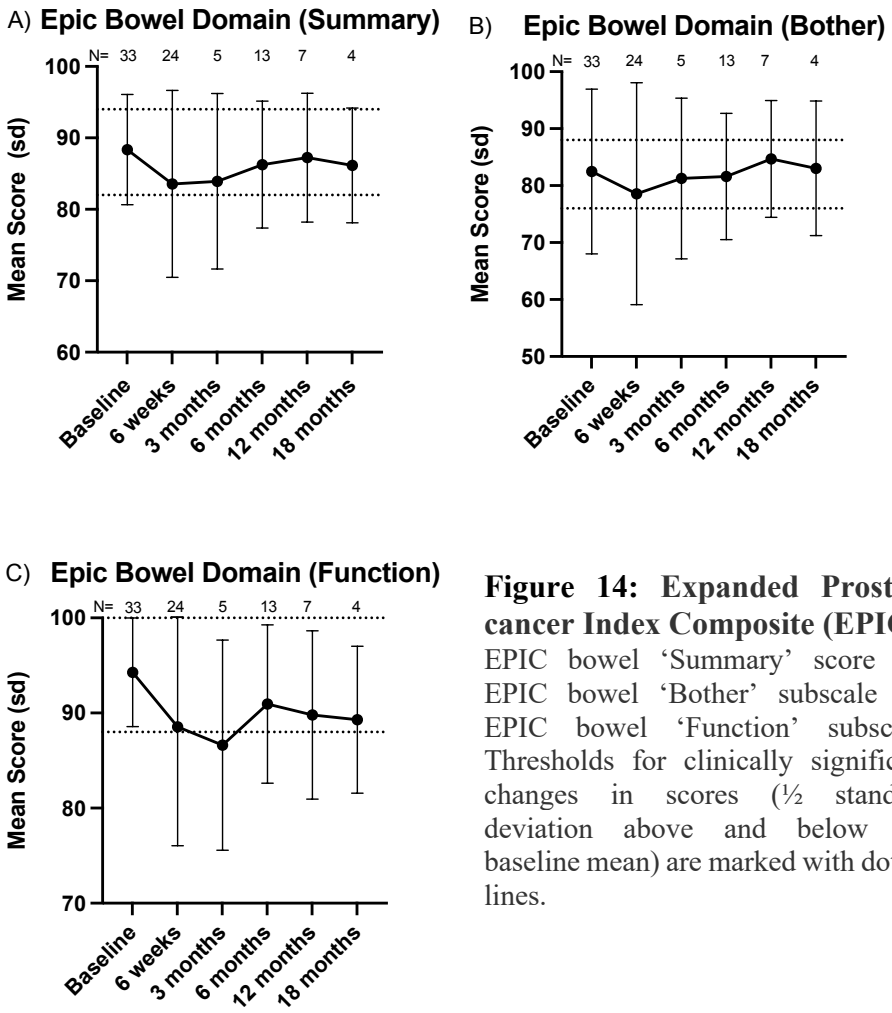


Figure 14: Expanded Prostate cancer Index Composite (EPIC)
EPIC bowel 'Summary' score A); EPIC bowel 'Bother' subscale B); EPIC bowel 'Function' subscale. Thresholds for clinically significant changes in scores (½ standard deviation above and below the baseline mean) are marked with dotted lines.

3.2.3.4 Oncological Outcomes

At the time of this analysis, two patients had undergone their 18-month repeat mpMRI and post treatment biopsy. Both patients had negative MRI scans (no lesion visible) and benign biopsy results with treatment effect identified at the targeted index lesion/treatment area and no cancer detected in the remainder of the non-treated prostate.

Baseline and post treatment PSA results are available for a cohort of 35 men, with a median follow up of 3 (IQR 2-10) months (Figure 15). Thirty-three (95%) patients demonstrated a PSA reduction following focal LDR brachytherapy. Amongst men with ≥ 3 months of PSA data, the mean decrease in PSA from baseline compared to last follow up was 73.85% (range 15.87-92.95%). One patient (2.8%), who had a F-GTV V100% of 99.98% and D90% of 293.52 Gy, demonstrated biochemical progression at 6 months.

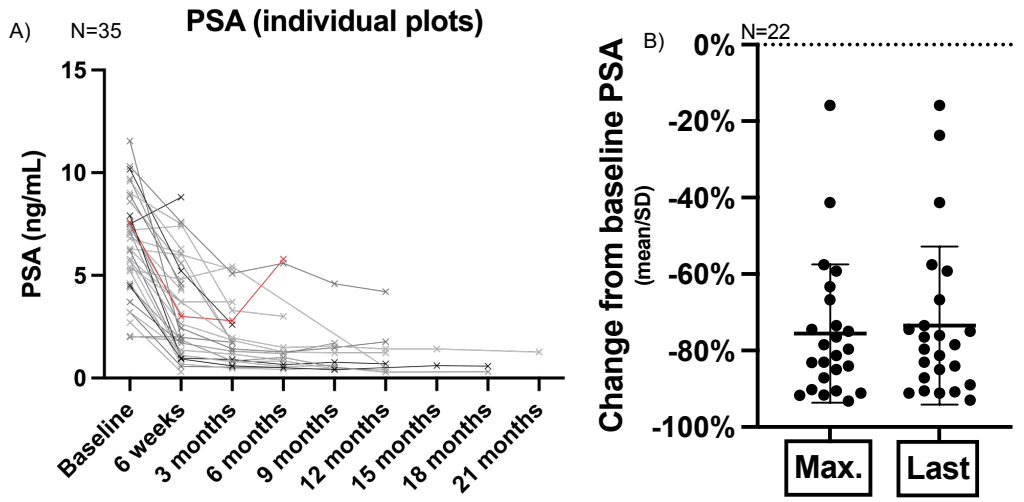


Figure 15: PSA outcomes following focal LDR brachytherapy.
A) Individual PSA progression, median [IQR] 3 months [2-10] B) Maximum and last change PSA from baseline as percentage, median [IQR] time to last PSA reading 9 months [3.75-12].

3.2.4 Discussion

Several studies have reported oncologic outcomes of focal brachytherapy [18,281,282,342,343] with a further five prospective studies currently in recruitment across Europe, North America and Australia – including a clinical registry (Australian and New Zealand Trials Registry, CTRN12619001669189, LIBERATE) [344-347]. Nguyen et al [333] treated 318 patients using selective brachytherapy to the prostate peripheral zone only. After 5.1 years of follow up, the reported biochemical recurrence free survival rate was 92% (Phoenix criteria). Cosset et al [281] analysed a cohort of 21 patients who underwent targeted focal brachytherapy for confirmed localized prostate cancer and found one patient had insignificant cancer outside the treatment zone at their 24 month assessment.. More recently, Kim et al found the 3-year biochemical recurrence-free survival to be 91.8% in a cohort of 30 men who underwent focal/partial

brachytherapy. This group also had significantly less genitourinary toxicity than a matched cohort of men who were treated with whole gland brachytherapy [343].

Quality of life data following LDR focal brachytherapy is sparse within the literature and mostly retrospective. Our preliminary analysis is based upon prospective data from approximately 40% of the completed cohort. The median length of follow-up across all metrics within this analysis is 5 months, as such there is minimal data available for the evaluation of this study's primary aims (18-month local control alongside 5-year biochemical progression free survival). Nevertheless, this review provides important prospective data regarding treatment related toxicity, patient-reported quality of life assessments and early cancer control outcomes.

The best method of determining patient sexual function has been shown to be self-reported techniques that enable more nuanced interrogation rather than laboratory-based diagnostic procedures [336]. Our analysis found that erectile dysfunction peaked in incidence and severity at 12 months with 45% of men experiencing some degree of toxicity, mostly grade 1. Men who reported grade 2 or grade 3 impairment typically had some degree of impairment at baseline, although larger numbers are required to validate this observation statistically. Based upon the analysis of IIEF-5 scores, this cohort of men had on average mild to moderate erectile dysfunction prior to receiving focal LDR brachytherapy suggesting that this group may have been more susceptible to higher grade toxicity. The overall impact of treatment appeared to be mild with the average change from baseline being a 2.5-point reduction in score. This is similar to the analysis performed by Cosset et al, that found in a similar focal LDR brachytherapy cohort, the mean decrease from baseline IIEF-5 to was 2 points following treatment [281]. Importantly, the potential for preservation of sexual function was determined by a 2016 expert panel to be a principal reason for choosing focal therapy over other modalities [348].

Regarding urinary function we observed acute grade 1 toxicity that peaked at 6 weeks post treatment and had resolved to baseline at 12 months. In contrast to 'Project 1', there was no grade 2 urinary toxicity reported. This may relate to a more refined implantation technique that uses less needles and brachytherapy seeds and targets a smaller F-PTV (cc). Keyes et al demonstrated that increased early urinary toxicity is associated with a greater number of implementation needles being used for whole gland brachytherapy [300]. Interestingly, patient's quality of life based on urinary function improved in more men than it worsened following treatment, this may reflect a reduction in prostate volume following focal brachytherapy that improves obstructive urinary symptoms. Prada et al identified a similar finding in a cohort of focal HDR brachytherapy patients that showed an improvement in IPSS scores following therapy [297].

Minimal rectal toxicity was identified in this study using the CTCAE grading scale however bowel function impairment following whole gland brachytherapy is well described [349]. Focal brachytherapy is targeted to areas of known disease and has been shown to cause less bowel symptoms than whole gland brachytherapy. Comparing matched cohorts of focal versus whole gland brachytherapy, Kim et al found that rectal toxicity occurred 50% less commonly with

focal treatment [343]. Analysis of the EPIC bowel domain subscale reveals that men found the symptom severity (function subscale) to be more detrimental to their quality of life then the annoyance associated with these side effects (bother subscale).

One difficulty for LDR brachytherapy is that formal dosimetric assessment criteria for focal LDR brachytherapy does not exist. Surrogate markers such as the British Columbia Cancer Agency criteria (BCCA) [314], although well known to the brachytherapy fraternity, are calibrated for whole gland treatment and not wholly suitable. Within the literature, the D90% and V100% are routinely reported by previous studies of Focal LDR brachytherapy [281,283,284]. In addition, a clinical trial of hemi-gland LDR brachytherapy reported dosimetry outcomes based on the V100% and D90% [327]. As such we have followed this reporting convention demonstrating post-implantation V100% ≥ 98% in 75% of patients. By following this reporting convention, we hoped to highlight the need for specific dosimetry criteria for focal LDR brachytherapy as well as allowing for comparisons to other studies.

In this analysis, two patients had progressed to their 18-month assessment of local cancer control that had shown benign results. The assessment of focal LDR brachytherapy effectiveness is complicated as interpreting prostate histology following radiation treatment is difficult. Pathologists typically rely on both architectural and cytoplasmic atypia. Following radiotherapy, cancer diagnosis is based almost solely on architectural features. This is because radiotherapy commonly induces cytoplasmic changes in benign tissue [320]. Architectural atypia that are suggestive for prostate cancer include: intraluminal crystalloids, blue mucin secretions, infiltrative growth, perineural invasion, the lack of corpora amylacea and high-grade PIN [350]. These histologic changes manifest slowly with cancer regression not usually seen before 12 months. Whilst understanding that complete histologic elimination of tumour can take up to three years post treatment [319]. Commonly, one of three histologic diagnoses can be assigned post radiotherapy: negative for malignancy, adenocarcinoma showing effect with no Gleason score assigned and adenocarcinoma showing no treatment effects with the appropriate Gleason score [351]. Of those patients described as having tumour with radiation effect but no Gleason score assigned, Cook et al found that they had a local failure rate of 18% over five years [323]. Gleason grading scores lack biological relevance post radiotherapy and should not be used as they lead to spurious higher-grade results [350]. Due to the intracellular effect of radiation on nuclear and cytoplasmic characteristics the Gleason grading system is not validated. Gleason grading can be used when there is no histologic evidence of radiation treatment effect [351].

The LIBERATE registry allows for the analysis of complimentary data from multiple quality of life assessments in conjunction with one another. Although based on a small sample size (4 patients) the divergence of physical and mental SF-12 scores at 18 months may represent the delayed morbidity that is traditionally associated with radiation-based therapies, such as worsening erectile function and rectal toxicity [352]. As the LIBERATE dataset continues to mature, this trend will be monitored and contextualised with further EPIC, IPSS and IIEF-5 results.

It is important to acknowledge the limitations of this preliminary analysis. The main limitation of this project relates to the lack of long-term follow up. Only a minority of patients have reached the 12-month assessment post treatment which restricts our interpretation of the data. As this dataset continues to mature, our results their potential implications will become more robust. Enrolment of patients to the LIBERATE registry has been hindered by the COVID-19 and this is outlined further in Section 2.4 'Impact of COVID-19 Pandemic'. Additionally, this registry is not powered for significant statistical analysis of its primary aims at this stage of recruitment and the analysis of its secondary aims was correspondingly narrow. Once recruitment for this registry is completed, determination of the oncological effectiveness of focal LDR brachytherapy in relation to 18-month local disease control and the rate of 5-year biochemical progression-free survival will progress the confirmation process of this emerging treatment modality. Ultimately, the lack of a comparison arm will limit the implications of this registry's outcomes. However, the LIBERATE registry will form a pivotal stage 2b 'exploration' study[306] that is needed to characterise relevant outcome measures prior to the undertaking of a major randomised trial.

3.2.5 Conclusion

This preliminary analysis of the LIBERATE registry provides prospective toxicity and quality of life data that outlines the real-world impact of focal LDR brachytherapy treatment. Namely, that a majority of men will experience acute urinary symptoms that self-resolve, rectal toxicity is minimal at all time points and that some men will experience mild to moderate sexual dysfunction. With ongoing recruitment to the LIBERATE registry, more robust data regarding oncological and functional outcomes will become available.

4. Discussion

Prostate cancer overdiagnosis and overtreatment has caused concern that men are needlessly being exposed to the side effects of whole-gland treatment. Although these traditional radical treatment options are oncological highly effective, there is often collateral damage to the surrounding tissue. With the improvement in imaging technology that can identify high risk lesions and a greater understanding of the 'index' lesion spread of metastatic disease, focal gland sparing techniques that offer comparable cancer control with less morbidity are gaining prominence. Spurred on by the successful paradigm shift in breast cancer treatment that has seen the traditional Halsted mastectomy replaced with local excision and reconstruction. The goal of focal LDR brachytherapy, that can direct radiation with millimetre accuracy, is to only ablate the foci of cancer within the prostate gland that will significantly impact the patient within their lifetime, maintaining as much normal tissue and function as possible.

Our current understanding of prostate cancer pathogenesis suggests that it is the largest cancer index lesion that determines the trajectory of the cancer. Informing this perspective, is the examination of 961 radical prostatectomy specimens undertaken by Ohori et al that found in the majority of cases, the grade/stage and most of the tumour volume is determined by the index lesion [207]. In addition, genetic studies suggest that metastatic or lethal prostate cancer arises from a monoclonal origin [21]. As such, if the index lesion can be accurately identified and treated then theoretically metastasis and death can be prevented. Although caution is still required, with post-treatment surveillance a vital component for ongoing patient care after focal therapy as biological exceptions have been identified. One case report tracked the genetic basis for a lethal clone of metastatic prostate cancer and found that it originated from a small, low grade (Gleason score 3) focus of tumour [353]. Although biologic variations of this nature would also contribute to treatment failure in men under active surveillance. Nevertheless, ablating a targeted index lesion with close post-treatment monitoring so if needed salvage treatment can be implemented in a timely and effective manner, forms the basis for prostate focal therapy.

Importantly, effective focal LDR brachytherapy depends on careful patient selection. Project 1 (Section 3.1) closely informed the eligibility criteria for Project 3 (Section 3.3) and incorporated a number of key principles (Section 3.3.2.5). Focal therapy has most utility treating intermediate risk prostate cancer with active surveillance prioritized in men with low-risk disease [200]. Often overlooked is a necessary assessment of the patient's personality which needs to be compliant and willing to engage in close surveillance after treatment. Another fundamental tenet is the advent of biopsy-based lesion identification which allows for the identified lesion within the prostate to be delineated and ablated. Although mpMRI technology has advanced, histologic confirmation is still required. The combination of mpMRI with targeted and systematic TP prostate biopsy enables a comprehensive interrogation of the gland. Ultimately, the effectiveness of focal therapy depends on appropriate patient selection. The LIBERATE registry provides a suitable template for focal LDR brachytherapy.

Collaborative post focal therapy follow up is integral to successful treatment. Due to the fact that healthy prostate tissue remains post therapy, the expectation is that the PSA will drop by 50-80%. Project 1 (Section 3.1) had a mean decrease in PSA following treatment of 72% although given there is variability, PSA as a marker of treatment success becomes less informative. Similarly, due to prostate inflammation from brachytherapy seed insertion, digital rectal examination may not be reliable. As such, monitoring should include mpMRI and targeted and systematic TP prostate biopsies that we recommend are undertaken at 18 months post treatment. In our experience this is the optimal timing to determine treatment success and allows for the best interpretation of post radiation prostate tissue histology.

While this thesis has demonstrated focal LDR brachytherapy to be a feasible and viable treatment option for low-intermediate risk prostate cancer, there are still many challenges to overcome. Further research is required to help identify all the truly lethal lesions within the prostate. Although contemporary evidence suggests that only the index lesion needs to be targeted concern exists regarding small or insignificant cancer at the time of focal treatment. New techniques to profile aggressive lesions within the prostate will improve patient selection and focal therapy effectiveness. Innovation in the area of functional and metabolic imaging, in combination with genetic biomarkers may allow for more accurate and appropriate ablation. Furthermore, there are economic considerations regarding focal LDR brachytherapy that need to be taken into account. In addition to the cost of post treatment monitoring, some men will have disease progression and require either further focal treatment or radical therapy leading to a double intervention cost, although this may be financially balanced out by the men that do not progress. It also may be deemed that focal therapy is cost effective given the benefit to the patient's quality of life that it allows. Further studies are required to discern these costs.

5. Conclusion

This study investigated focal LDR brachytherapy for the treatment of low-intermediate risk prostate cancer in an Australian context. Through the combination of three projects, it sought to describe the 'viability' and 'feasibility' of this treatment modality. Viability refers to a capability assessment of focal LDR brachytherapy and includes oncological effectiveness, functional and toxicity outcomes and salvage options if required. Feasibility refers to an assessment of practicality for the implementation of focal LDR brachytherapy and comprises technical and procedural variables.

Project 1 reviewed questions of feasibility relating to lesion targeting techniques, practical dosimetry considerations and the definition of treatment success. It also added, via analysis of the largest retrospective cohort reported in the literature to date, further evidence that focal LDR brachytherapy is viable with encouraging oncological and functional outcomes.

Project 2 in proof-of-concept report assessed the feasibility of salvage robot assisted radical prostatectomy following focal LDR brachytherapy and showed it to be a safe procedure with no increase in technical difficulty. This validates a key principle of viability for focal LDR brachytherapy, namely that if required salvage intervention post treatment is possible.

Project 3, although a preliminary analysis, provides a foundational framework for the practical implementation of focal LDR brachytherapy providing feasible patient selection, treatment methodology, dosimetry parameter and post-treatment monitoring templates. In addition, it reports prospective toxicity and quality of life data that outlines the real-world impact of focal LDR brachytherapy treatment and its viability as a treatment modality.

In summary, this thesis has demonstrated that focal LDR brachytherapy can ablate clinically significant cancer. Validated and reproducible monitoring of the target area and uninvolved parenchyma is possible and practical. Treatment related toxicity appears to be mild with a majority of men experiencing acute urinary symptoms that self-resolve. Salvage surgical treatment appears not to be impaired by primary focal LDR brachytherapy and is a viable option in the case of treatment failure. With the continuing maturation of the LIBERATE registry, the viability and feasibility of focal LDR brachytherapy can be further determined, establishing the basis for a future randomized control trial investigating this treatment modality.

6. References

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7. Appendix

APPENDIX A: Focal LDR Brachytherapy Technique Protocol

Treatment aim and rationale

The major goal of prostate brachytherapy is to deliver a tumoricidal dose to the cancer-bearing prostate while minimising urinary and rectal morbidities, however focal brachytherapy aims to deliver radiation dose focused around the index lesion. Specific aims in this setting are to design an optimal treatment plan using 3D anatomical information, to implement the treatment plan with precision, and to analyse the dosimetric outcome post implantation. A standard 3 phase implant technique ("Seattle Based Methodology") will be used, comprising a pre-plan volume study for the purpose of brachytherapy planning, followed by seed implantation 4-12 weeks later. At Day 1 post implantation, a non-contrast CT scan of the true pelvis will be acquired for the purpose of assessing implant quality and determining dose to organs at risk.

Simulation (Volume Study)

Patient Preparation

Patient will be required to stop any anti-coagulant therapy at least 5-10 days prior to theatre procedure and departmental fasting and bowel preparation will need to be adhered to for a routine volume study. A pre-plan volume study using TRUS probe will be performed by a credentialed RO approximately 4-12 weeks prior to implantation. The procedure will either be performed under general anaesthesia or light sedation in one of the main theatres at one of the nominated Epworth Healthcare sites.

Positioning and Immobilisation

Patients will be placed in an extended lithotomy position with their pelvis positioned in a midline configuration. Following a perineal wash, an Indwelling Catheter (IDC) will be placed in the bladder and closed with a spigot.

1. Pubic arch

   The first consideration in the positioning and immobilisation process is to determine the degree of pubic arch interference. The pubic arch may ''shadow'' the anterior and lateral portions of the prostate, making it difficult or impossible to implant seeds in these locations. If this restriction exists, the RO may angle the template and ultrasound probe assembly to achieve better needle access. Severe pubic arch interference is considered a contraindication for performing the implant. As focal brachytherapy is only targeting the index lesion, pubic arch interference is not expected to be an issue in these cases.

2. Urethra

   The prostatic urethra is readily visualised on TRUS when a catheter is left indwelling during imaging. In order to plan the treatment to avoid direct implantation near the urethra or to calculate the dose received by the urethra, the entire length of the prostatic urethra needs to be visualised and captured on ultrasound images.

3. Rectum

   The anterior wall of the rectum is adjacent to the prostate, which makes it difficult to deliver the prescribed dose to the posterior periphery of the prostate without delivering an equivalent dose to the most anterior portion of the rectum. Particular attention is given to the recto-prostatic interface in planning the implant. The RO aims to cover the entire volume of interest, while keeping the volume of the rectal wall that receives the prescribed dose as small as possible.

Simulation Procedure

A TRUS probe will be inserted into the rectum under longitudinal view and manoeuvred to lie as parallel to the longitudinal axes of the visible urethra as achievable. In trans-axial imaging the posterior row is selected and placed 2-3mm inside the posterior prostate ensuring minimal compression and prostate deformation. Following set-up, the index lesion, as determined on mpMRI, will be reviewed to determine its sonographic characteristics. Following image capture assessment of pelvic geometry and acquisition of gland length, width and height will be taken and recorded including an assessment of the integrated whole prostate volume for the purpose of comparison with other prior image datasets.

Ultrasound Requirements

Equipment for ultrasound-guided prostate implants includes the ultrasound machine, the rectal probe, the stepping device/probe carrier, the perineal template, and the stabilising mechanism. The ultrasound machine is a portable unit that contains a seed implant software package such that a grid pattern can be displayed on the screen. The stepping device allows the rectal probe to be attached to the stabilising mechanism while permitting movement in and out of the patient's rectum in precise steps. The needle template has holes accepting 17 gauge or 18 gauge needles designed to mount directly on the probe carrier, in which case it remains stationary with respect to the perineum as the probe is moved. The holes on the needle template correspond to the grid points displayed on the TRUS monitor screen. The stabilising mechanism immobilises the entire rectal probe/carrier/template system against the operating table or floor, to prevent unintentional motion of the probe and needle template during the implant procedure. The template is placed at close proximity to the perineum to minimise needle splaying in the target volume. Trans-axial images (2.5-5.0mm) will be acquired from 0.5mm above base of prostate finishing 10.0mm below the visible penile bulb and auto-captured within the intra-operative module of Variseed™ treatment planning system.

Treatment Planning and Dosimetry

Pre-planning (Seed Distribution)

In order to assess the amount and distribution of radioactivity it is essential to have an accurate measurement of prostate volume. The volume estimation can be combined with the volume

measure on mpMRI and preplanning. The patient is placed in the lithotomy position identical to that be used for the subsequent implant procedure and 2.5-5mm ultrasound sections taken of the prostate from base to apex using the stepping unit. Implants will be planned with Iodine 125 which has a half-life of 59 days, and a prescribed dose of 145Gy which is the minimum peripheral dose to the margin of the target volume specified. Different types of seed distributions are in current use and a consensus on the optimal seed distribution does not exist. The classic approach is to space the seeds 1 cm apart, centre-to-centre, throughout the prostate. This approach, referred to as *uniform loading*, requires a higher number of lower strength seeds ~typically 0.4 to 0.5 U seed for I-125 and is characterised by relatively high doses in the centre of the prostate. In *modified peripheral loading*, some seeds in the central portion of a uniformly loaded implant are deleted to reduce the central dose. This may require increasing the strength of the remaining seeds or decreasing the needle to needle or seed to seed spacing in the periphery. *Peripheral loading* is an alternative approach in which the seeds are preferentially limited to the periphery of the prostate. This requires a substantial increase in seed strength ~typically 0.75 to 1.0 U/seed for I-125. The end result is to produce a dose minimum, albeit above the prescribed minimum dose, instead of a dose maximum, at the location of the urethra.

Planning System Requirements

Prostate mapping will be performed 4-12 weeks before implantation by TRUS using a BK ProFocus (BK Medical ApS, Herlev, Denmark) at 6-12MHz. Images will be recorded every 2.5-5mm and downloaded to the VariSeed™ treatment planning system (Varian Medical Systems, Inc., Palo Alto, CA).

CT Import and Secondary Image Co-registration

The mpMRI datasets will be downloaded and imported into Varian's Variseed™ treatment planning system (Varian Medical Systems, Palo Alto, CA) from either Intelerad® InteleViewer™ (Intelerad Medical Systems, Montreal, QC, Canada) or CD-ROM (DICOM format) (when applicable).

A fusion will occur between the T1W or T2W MRI dataset and acquired pre-planning ultrasound volumes using the fusion module within Variseed™. Intra-prostatic fiducials including IDC and gland perimeter will ensure a tight match based on Cartesian alignment and X-roll pitch adjustment. The fusion will be performed by a senior RO and then verified by either a senior Radiation Therapist (RT) or Radiation Oncology Medical Physicist (ROMP).

Contouring

Target volume definition:

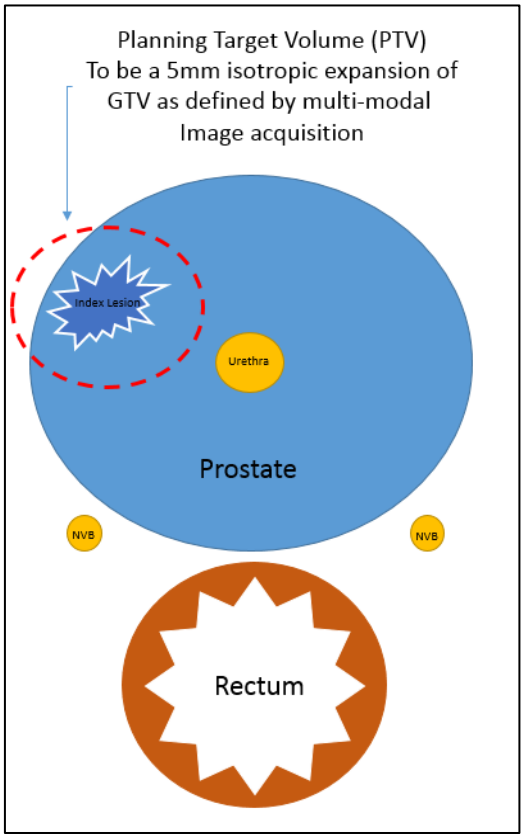
1) Gross Tumour Volume (GTV)

Both mpMRI and TRUS based sonographic information will be used for tumour and critical structure definition. The Gross Tumour Volume will include the radiologically defined extent of the index lesion acquired from multi-modal imaged based information.

2) Clinical Target Volume (CTV)

The Clinical Target Volume will not be defined. The anticipated margin for microscopic extension of index lesion related disease will be incorporated via a single isotropic expansion of the GTV in the determination of PTV.

3) Planning Target Volume (PTV)



The Planning Target Volume will be determined by a 7mm isotropic expansion of the GTV as performed as an advanced manipulation within the contouring tab of Variseed™ (see above Figure). This margin has been determined by Polders et al to provide a robust coverage of a focal target volume taking into account systematic uncertainties inherent within imaging modalities and post-acquisition image manipulation including fusion. In the event of a posteriorly located nodule adjacent to the rectum, the posterior GTV-PTV expansion will be 0mm.

Critical Organ Definition

For rectal and urinary morbidities, the critical organs are considered to be the anterior rectum and the prostatic urethra, respectively. These structures will be defined as follows:

1) Rectal Wall

Pre-plan: The entire rectum will be contoured on ultrasound images acquired from volume study.

Post-implant: The rectum will be contoured on all CT scan slices where radioactive seeds are visible. Both the inner and outer walls will be contoured.

2) Urethra

Pre-plan: The prostatic urethra is readily visualised on TRUS when a Foley catheter is left indwelling during imaging. In order to plan the treatment to avoid direct implantation near the urethra or to calculate the dose received by the urethra, the entire length of the prostatic urethra will be visualised and contoured during pre-plan.

Post-implant: The urethra will be contoured as a structure on each slice where seeds can be seen. The wall should be identified by either catheterisation or fusion with transrectal ultrasound.

Prescription

The total radiation dose for the entire cohort will be 145Gy LDR via a single monotherapy implant with the 145Gy encompassing the annotated PTV as determined in section 7.3.4.1. Prescribed doses will be according to TG 43 TG-43U1 report by the American Association of Physicists utilising I^{125} Amersham brachytherapy seeds (model 6711) in a range of activities from (0.311mCi – 0.500mCi) on day of implantation.

Planning Technique

Planning of the I^{125} seed treatment is carried out with the intent of covering the 100% isodose. Some contiguity (linkage) of the 150% isodose is desired particularly if over known sites of biopsy proven or radiologically evident disease, provided the 150% isodose is not overlapping the urethra or rectum. There should be minimal contiguity of the 200% isodose line in all instances.
Seed moiety may include the use of single seeds, back-to-back seeds and other non-standard loads to satisfy dosimetric objectives. Stranded seeds will be exclusively used to minimise the risk of embolisation. Care to avoid co-ordinates that overlap with the pre-defined pubic arch will be required. All treatment plans will have an independent check by a secondary ROMP or RT. This check must include all relevant patient demographics, seed activity, seed placement, spatial dose distribution, dosimetric indices and perform a manual calculation, typically based on a nomogram.

Dose Distribution and Reporting Requirements

PTV dose objectives are outlined in the table below:

Priority	**Target**	**Dose-volume objectives (145Gy)**
1	**PTV**	V100% $\geq$ 98%
		V150% $\leq$ 40-65%
		D90 > 145Gy

Normal Tissue Tolerances/Dose Constraints

Normal tissue dose-volume constraints are as follows:

Priority	**Normal tissue**	**Dose-volume constraints (145Gy)**
1	**Urethra**	D10% < 150% of prescription dose
		D30% < 130% of prescription dose
2	**Rectum***	D2cc < 145Gy
		D0.1cc < 200Gy

*If rectal constraints are exceeded patient will be implanted with a rectal spacer (SpaceOAR hydrogel).

Seed Implantation

Treatment Equipment Specifications

Treatments will be carried out in accordance with department policy and using the appropriate verification protocols. Intra-operative real time implants will be performed using the integrated Variseed™ TPS articulated with a digital stepper and Barzell-Whitmore floor mounted stabiliser using a high resolution biplanar ultrasound probe (5-12MHz) (B&K Flex Focus 700).

Patient Preparation and Implantation

Implantation will occur under general anaesthetic or light sedation and a full pre-anaesthetic risk adapted work-up according to department policy. Patients will be placed in an extended lithotomy position and antibiotic prophylaxis will be given. A real time implant will be overseen following concordance with the set-up positioning as per pre-plan. Seeds will be inserted with ultrasound guidance. Fluoroscopic verification will be used where necessary. Urethral identification will be via IDC. Full radiation protection measures will be followed as per departmental guidelines. Real-time dosimetric analysis will be conducted via the RTI module within Variseed™ TPS. Additional 'zulu' seeds will be inserted should clinically meaningful deviation from the intended plan be suspected.

For posterior targets adjacent to rectum, following completion of the implant, SpaceOAR® gel will be implanted via an additional transperineal injection into the posterior prostatic space providing this can be satisfactorily identified and hydro-dissected. SpaceOAR® hydrogel is a commercially available system that is on the Australian Register of Therapeutic Goods (ID 179172). It is injected as a liquid between the prostate and rectum under ultrasound guidance, solidifying within seconds into a hydrogel that pushes the anterior rectal wall away from the high dose region that envelopes the prostate. The hydrogel is biocompatible and maintains a consistent space over a 3-6 month period, during which a typical LDR period of irradiation would take place. After 6 months, the hydrogel liquefies, allowing it to be absorbed into the body and then cleared. Use of SpaceOAR hydrogel in this setting is considered to be standard of care.

Seed Delivery/Verification

Seed Calibration

A minimum of five seeds will be assayed for each pre-loaded patient kit. A well-type ionisation chamber and electrometer with a calibration traceable to an accredited standards laboratory will be used for this purpose. Source strength measurements will be undertaken upon arrival of the pre-loaded kits to the department. This will be carried out in accordance with the AAPM TG-56 recommendations. An accuracy check of the calibration equipment is performed at least every 6 months using a NIST traceable secondary seed standard (I-125). The reading is corrected for ambient conditions. The measurement result should be within 2% of the decay corrected certificate value.

The mean source strength of the measured sources should agree to within 3% of the manufacturer's stated source strength and the absolute difference of all the individual source measurements are within the quoted calibration uncertainty on the manufacturer's certificate. If the mean difference is greater than a 3% tolerance level, the source of the discrepancy will be investigated and independently verified by a repeat set of measurements by a second Medical Physicist. A difference of 5% between the measured and mean source strength and manufacturers values should be discussed with the manufacturer.

QA procedures

Our LDR Brachytherapy program has established a quality assurance process and accompanying documentation to ensure the accuracy of treatment delivery. Beyond the initial commissioning of the system, the medical physics team is involved in every aspect of the process prior to patients commencing treatment to ensure accuracy and safety of the treatment delivery. This includes, but is not limited to, patient-specific quality control procedures (validation of treatment plans, data integrity, source strength verification), equipment QA (including ultrasound fidelity and attendance during implantation where requested) and radiation safety. The radiation therapy team will perform the role of plan verification and implant delivery. It is their responsibility to ensure that the patient specific LDR QA report (indicating all the quality assurance processes used to validate the treatment plan) is recorded and approved. In terms of ensuring compliance with the current protocol, the current protocol has been designed to ensure all processes are in line with standard management.

Dosimetry Review

Plan quality assurance reviews are an essential part of standard clinical practice within radiation oncology services to ensure the accurate and safe delivery of radiation therapy treatments. Each participant's plan review will be documented in the medical record. When a plan does not pass the acceptance criteria, the reasons must be analysed and replanning must be considered.

Postoperative dosimetry

There are a number of potential indices of implant quality but as yet insufficient long-term follow-up data to confirm the value of all those proposed. It is recommended that the following indices are recorded for all patients:

1. The volume implanted.
2. The number of seeds used.
3. The number of needles used.
4. The total activity implanted.
5. The prescribed dose.
6. The D90, that is, the dose that covers 90% of the PTV as defined from post implant imaging.
7. The V100%, that is, the volume of the PTV that has received the prescribed dose.
8. V150%, the volume of the PTV that has received 50% more than the prescribed dose.

Post-implant computerised tomography-based assessment will occur the day after seed implantation.

A non-contrast pelvic CT utilising 5mm slice thickness will be obtained from the L5/S1 interface down to 10cm below the obturator foramina. The post plan assessment will occur in the Variseed™ TPS environment and relevant coronal and sagittal reconstructions attended. The post plan CT will occur with a silastic IDC inserted to assist with urethral identification. Seed identification will utilise a combination of manual check from orthogonal digitally reconstructed radiographs (DRR) confirmed with the seed finder module® locating within Variseed™. The post-plan will be fused with the pre-plan volume study for the purpose of PTV reconstitution and urethra identification. The whole rectal contour spanning the length of the prostate will be separately contoured.

The final plan will be reviewed by the treating RO, RT and ROMP to ensure quality parameters are met. If quality parameters are not met, remedial action in the form of further brachytherapy, external beam radiotherapy or prostatectomy may be considered where appropriate.

Prostate dosimetry will be stratified according to British Columbia Cancer Agency criteria, as outlined in the below table (Nasser et al 2015):

PTV	Goal	Sub-optimal	Poor
V100	>85%	75 -85%	<75%
D90	>90%	80-90%	<80

Treatment Deviations and Violations

All participant plans must be checked to ensure quality during the planning stage, to minimise treatment delivery deviations and violations. Protocol specific deviations and violations are outlined in the table below and will be recorded in the registry.

Deviation		**Violation**	
Prescription			
Difference in prescribed or calculated dose within 6-10% of 145Gy		Difference in prescribed or calculated dose greater or less than 6-10% of 145Gy	
Target Volumes and Organs at Risk			
-		Any isotropic/anisotropic GTV to PTV expansion contrary to that stipulated in Section 7.3.4.1.	
-		Any portion of the identified GTV not included in the treated volume	
Organs at risk not contoured as per protocol		Organs at risk not contoured as per protocol and dose constraints exceeded	
Dose Constraints (pre-plan)			
PTV	-	PTV	V100% < 98%
	-		V150% < 70%
	-		D90 < 145Gy
Urethra	-	Urethra	D10% ≥ 150%
	-		D30% ≥ 130%
	-		D0.1cc > 200Gy

Other	
Usage of other manufacturer seeds	-
-	5α-reductase inhibitor not ceased and PSA level not assessed prior to implant

Follow up	
Implant occurring 12-16 weeks after conduct of the volume study	Implant occurring greater than 16 weeks after conduct of the volume study
PID scan occurring between Day 2-30 (inclusive) following LDR implant	PID scan occurring after Day 30 following LDR implant
Scheduled follow up appointment with radiation oncologist occurring greater than 2 weeks (1.5 and 3 month appointments) or a month (all other appointments) outside planned date	-

Treatment Delivery

Implant Interruptions and Delays

Implant is intended to be delivered approximately 4-12 weeks post Volume study. Any delay longer than 12 weeks must be noted with explanation and will be considered a deviation.

Accepted Considerations

Spinal anaesthetic is acceptable for the purposes of the volume study and LDR implant. Post implant CT for the purpose of dosimetry review for this study is scheduled for Day 1. A delay of up to Day 30 is considered acceptable.