The Oncological Outcomes of Dose Escalated Radiotherapy and its Impact on Biochemical Control and Toxicity in Men with Prostate Cancers

A thesis submitted for Doctor of Medical Science (by compilation of published papers)

Dr Michael Wan Tien CHAO
MBBS (Hons) AFRACMA FRANZCR
Orcid No: 0000-0002-3497-3746

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Abstract

Introduction:
Radiation therapy (RT) for prostate cancer (PC) has steadily evolved over many years, with improvement in biochemical relapse free survival (bRFS). An association between overall survival and doses ≥ 75.6 Gray (Gy) in men with intermediate and high-risk PC has been reported in population-based studies. Contemporary RT techniques such as image guided radiotherapy, intensity modulated radiotherapy, and stereotactic body radiotherapy, has facilitate further dose escalation. Brachytherapy is an internal form of RT that also developed substantially and can be delivered in combination with external beam radiation therapy (EBRT). However, dose escalation can come with increased gastrointestinal (GI) toxicity and new devices such as rectum spacers have been developed to spare this critical normal structure.

Methods:
Our large prospective brachytherapy database, that I created, which included patients treated with low dose rate (LDR) and high dose rate (HDR) brachytherapy was interrogated to determine the long-term oncological outcomes. In addition, I was one of the first radiation oncologists in Australia to use a novel polyethylene glycol hydrogel rectal spacer and its iodinated counterpart. We were able to implement its use as a fiducial marker in the post-prostatectomy setting and its use as a tissue expander in the intact prostate for EBRT with or without high dose rate brachytherapy as well as in the post-prostatectomy setting.

Results:
I found that the use of LDR and HDR brachytherapy with or without EBRT to be safe and efficacious. The bRFS for LDR brachytherapy alone for low to intermediate risk PC was excellent as was its use in combination with EBRT for men with predominantly unfavorable intermediate risk PC. In addition, the use of HDR brachytherapy in combination with EBRT for men with intermediate and high-risk PC also yielded excellent bRFS comparable to any other series reported in the literature. I successfully introduced the use of hydrogel spacers into our practice with marked reduction in rectal volumes irradiated to high radiation doses which allowed appropriate dose escalation of EBRT with or without HDR brachytherapy. This has translated to a marked reduction in late GI toxicity. In addition, we also successfully used hydrogel spacers in the post-
prostatectomy setting both as a spacer to allow for ultra-high dose radiation therapy and as a fiducial marker with hydrogel spacer in its iodinated form.

**Conclusion:**
Although the use of brachytherapy has declined in the last few years, our results confirm its outstanding efficacy in PC and as such we will continue to advocate for its use. We will continue to support a brachytherapy unit for the treatment of PC. In addition, my work on hydrogel spacers has resulted in its use as standard practice in all PC patients who require EBRT.
Declaration

The following declaration is signed by the student: This is to certify that:

i. The thesis comprises only my original work towards the Doctor of Medical Science except where co-authorship is indicated in (2.) Published articles that form this thesis,

ii. Due acknowledgement has been made in the text to all other material used

iii. The thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Signature: ..............................................................
Preface

Original research publications:

(Contribution of Chao M outlined for each publication)


   *Chao M contribution – 55%, Sandy Spencer and Danielle Healy assisted with data collection*


   *Chao M contribution – 65%, Sandy Spencer assisted with data collection*


   *Chao M contribution – 60%, Sandy Spencer and Huong Ho assisted with data collection*


   *Chao M contribution – 65%, Sandy Spencer and Huong Ho assisted with data collection*


*Chao M contribution – 55%, Huong Ho assisted with data collection*


*Chao M contribution – 60%, Sandy Spencer and Huong Ho assisted with data collection*


*Chao M contribution – 60%, Sandy Spencer and Huong Ho assisted with data collection*


*Chao M contribution – 60%, Huong Ho assisted with data collection and analysis*

As the lead author for the above publications, Chao M contributed greater than 55% of the bodies of work, with specific proportion of contributions to each study outlined above. Chao M made substantial contributions to each of literature search, study design, protocol development, data collection, data analysis, manuscript preparation, manuscript editing and revision. Chao M was the principal investigator in the human ethics approved studies that prospectively collected the patient information and follow up data that was used in the above studies. Sandy Spencer, Huong Ho and Danielle Healy assisted with data collection as outlined above. In addition, Chao M was the first author and corresponding author on the published manuscripts.
Background Publications:


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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>3DCRT</td>
<td>3-Dimensional Conformal Radiation Therapy</td>
</tr>
<tr>
<td>ADT</td>
<td>Androgen Deprivation Therapy</td>
</tr>
<tr>
<td>ALARA</td>
<td>As Low As Reasonably Achievable</td>
</tr>
<tr>
<td>AP</td>
<td>Anterior-Posterior</td>
</tr>
<tr>
<td>ASCENDR-RT</td>
<td>Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy</td>
</tr>
<tr>
<td>bPFS</td>
<td>biochemical Progression Free Survival</td>
</tr>
<tr>
<td>bRFS</td>
<td>biochemical Relapse Free Survival</td>
</tr>
<tr>
<td>CBCT</td>
<td>Cone Beam Computerised Tomography</td>
</tr>
<tr>
<td>CHHiP</td>
<td>Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer</td>
</tr>
<tr>
<td>CTV</td>
<td>Clinical Target Volume</td>
</tr>
<tr>
<td>DFS</td>
<td>Disease Free Survival</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>DRE</td>
<td>Digital Rectal Examination</td>
</tr>
<tr>
<td>DVH</td>
<td>Dose Volume Histograms</td>
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<td>EBRT</td>
<td>External Beam Radiation Therapy</td>
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<tr>
<td>FFFB</td>
<td>Freedom from Biochemical Failure</td>
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<tr>
<td>G</td>
<td>Grade</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<tr>
<td>GU</td>
<td>Genitourinary</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray</td>
</tr>
<tr>
<td>HA</td>
<td>Hyaluronic Acid</td>
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<tr>
<td>HDR</td>
<td>High Dose Rate</td>
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<tr>
<td>HDRT</td>
<td>High Dose Radiation Therapy</td>
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<tr>
<td>HIFU</td>
<td>High Intensity Focused Ultrasound</td>
</tr>
<tr>
<td>HS</td>
<td>Hydrogel Spacer</td>
</tr>
<tr>
<td>HYPRO</td>
<td>Hypofractionated Irradiation for Prostate Cancer</td>
</tr>
<tr>
<td>IGRT</td>
<td>Images Guided Radiation Therapy</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiation Therapy</td>
</tr>
<tr>
<td>LDR</td>
<td>Low Dose Rate</td>
</tr>
<tr>
<td>LDRT</td>
<td>Low Dose Radiation Therapy</td>
</tr>
<tr>
<td>LR</td>
<td>Left-Right</td>
</tr>
<tr>
<td>MFS</td>
<td>Metastatic Free Survival</td>
</tr>
<tr>
<td>MID</td>
<td>Minimally Important Difference</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Memorial Sloan Kettering Cancer Centre</td>
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<tr>
<td>OS</td>
<td>Overall Survival</td>
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<tr>
<td>PC</td>
<td>Prostate Cancer</td>
</tr>
<tr>
<td>PCRSG</td>
<td>Prostate Cancer Research Study Group</td>
</tr>
<tr>
<td>PEG</td>
<td>Polyethylene Glycol</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression Free Survival</td>
</tr>
<tr>
<td>PIVOT</td>
<td>Prostate cancer Intervention Versus Observation Trial</td>
</tr>
<tr>
<td>PPRT</td>
<td>Post Prostatectomy Radiation Therapy</td>
</tr>
<tr>
<td>PROFIT</td>
<td>Prostate Fractionated Irradiation Trial</td>
</tr>
<tr>
<td>PROTECT</td>
<td>Prostate Testing for Cancer and Treatment</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>QUANTEC</td>
<td>Quantitative Analyses of Normal Tissue Effects in the Clinic</td>
</tr>
<tr>
<td>RALP</td>
<td>Robot Assisted Laparoscopic Prostatectomy</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>RFS</td>
<td>Relapse Free Survival</td>
</tr>
<tr>
<td>RP</td>
<td>Radical Prostatectomy</td>
</tr>
<tr>
<td>RT</td>
<td>Radiation Therapy</td>
</tr>
<tr>
<td>RTOG</td>
<td>Radiation Therapy Oncology Group</td>
</tr>
<tr>
<td>rV</td>
<td>rectal Volume</td>
</tr>
<tr>
<td>SBRT</td>
<td>Stereotactic Body Radiotherapy</td>
</tr>
<tr>
<td>SEER</td>
<td>Surveillance, Epidemiology, and End Results Program</td>
</tr>
<tr>
<td>SI</td>
<td>Superior-Inferior</td>
</tr>
<tr>
<td>TFM</td>
<td>Tissue Fiducial Marker</td>
</tr>
<tr>
<td>TRUS</td>
<td>Transrectal Ultrasound</td>
</tr>
<tr>
<td>VMAT</td>
<td>Volumetric Arc Therapy</td>
</tr>
<tr>
<td>VUA</td>
<td>Vesico-Urethral Anastomosis</td>
</tr>
</tbody>
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1 Introduction and Overview

1.1 Prostate Cancer
Prostate cancer (PC) is the most common cancer among Australian men (excluding skin cancer) and the second commonest cause of cancer related deaths. A recent Australian Government publication reported that there were 19,508 new cases reported in 2019 (1). This represented an increase of 79 new cases per 100,000 males in 1982 to 130 per 100,000 in 2019. This increase is expected to continue due to increases in the number of men presenting for testing, changes in diagnostic practices and the ageing population. Although the mortality rates are declining, it still represented 3159 deaths (or 25.3 per 1,000,000) in 2015 being the fourth leading cause of all deaths among Australian males. In 2006-2010, the 5-year survival is expected to be 92% (1).

1.2 Prostate Cancer Risk Stratification
Following a prostate cancer diagnosis, patients are faced with a multitude of care options, the advisability of which is influenced by patient factors and by the cancer’s severity or aggressiveness. The ability to categorise patients based on cancer aggressiveness is invaluable for facilitating care decisions. After the diagnostic biopsy and appropriate initial staging has demonstrated localised prostate cancer, risk stratification of prostate cancer severity or aggressiveness should include prostate specific antigen (PSA), clinical stage rectal examination (DRE), Grade Group, amount of cancer on biopsy (number of cores involved and maximum severity of any single core) and imaging. A practical rationale for care stratification by these core risk groups is that they are broadly used in contemporary practice (2, 3), and they are based on criteria (PSA, DRE, Gleason score or Group Grade) that have been the cornerstone of eligibility or risk stratification in randomised and prospective multicentre studies that constitute the basis of treatment guideline recommendations (see Table 1).
### Table 1: Prostate Cancer Risk Groups

<table>
<thead>
<tr>
<th>Risk Groups</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low Risk</td>
<td>PSA &lt;10 ng/ml and Grade Group 1 and clinical stage T1-2a and &lt;34% of biopsy cores positive and no core &gt;50% involved</td>
</tr>
<tr>
<td>Low Risk</td>
<td>PSA &lt;10ng/ml and Grade Group 1 and clinical stage T1-2a</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>PSA 10-&lt;20ng/ml or Grade Group 2-3 or clinical stage T2b-c</td>
</tr>
<tr>
<td></td>
<td>Favourable: Grade Group 1 (with PSA 10-&lt;20 or Grade Group 2 (with PSA &lt;10)</td>
</tr>
<tr>
<td></td>
<td>Unfavourable: Grade Group 2 (with either PSA 10-&lt;20 or clinical stage T2b-c) or Grade Group 3 (with PSA &lt;20)</td>
</tr>
<tr>
<td>High Risk</td>
<td>PSA ≥ 20ng/ml or Grade Group 4-5 or clinical stage ≥ T3</td>
</tr>
</tbody>
</table>

### 1.3 Prostate Cancer Management Options

The management options for each localised prostate cancer risk group can include active surveillance, radical prostatectomy or radiotherapy (RT) with or without androgen deprivation therapy (ADT). For very low risk and low risk disease, active surveillance is recommended for most patients. However definitive treatment with either radical prostatectomy or radiotherapy may be offered. ADT should not be given along with radiotherapy with the exception of downsizing the prostate for brachytherapy. For intermediate risk disease, radical prostatectomy or radiotherapy with ADT are standard treatment options. Patients with favourable intermediate risk disease can be treated with radiotherapy alone. In selected intermediate risk patients, other treatment options may be considered such as cryotherapy, focal therapy or high intensity focussed ultrasound (HIFU) but these interventions are not the standard of care. In high risk disease, radical prostatectomy or radiotherapy with ADT are standard treatment options.

### 1.4 Active Surveillance

Active surveillance aims to avoid unnecessary treatment in curable men with low risk PC by treating only those showing signs of progression (4). This may also be discussed for subgroups of patients with intermediate risk PC (5). These must be followed with frequent PSA controls and a secondary biopsy after one year or at PSA rise. If the PC shows signs of progression, radical treatment may be offered if the patients are healthy enough to undergo treatment.

### 1.5 Radical Prostatectomy

Open radical prostatectomy (RP), with surgical removal of the prostate gland and usually the seminal vesicles, is usually performed with a retropubic access through a midline incision, although a perineal access is an option. In 1947, Millin et al. carried out retropubic prostatectomy, followed
by Memmelaar et al. with the first radical retropubic prostatectomy in 1949 (6-8). However, it was not until the 70s and 80s when Walsh et al. reported his techniques of anatomical and physiological RP, that complication rates plummeted (9).

In recent years, the minimal invasive techniques of laparoscopy and robot-assisted laparoscopic prostatectomy (RALP) has gained popularity with robot-assisted techniques being the most frequently used (10). The development of these techniques has resulted in shorter hospitalization and faster rehabilitation compared to open prostatectomy (11). However, it is unclear whether the minimal invasive techniques result in better oncological long-term results and less late complications than open surgical techniques.

Regarding complications of RP, perioperative mortality is very low (0-1.5%) (12). Major perioperative complications are also rare, but the most common include urinary fistulas, damage to the rectum, major bleeding, deep venous thrombosis and pulmonary embolism. The main problems of surgery are the long-term side effects in form of persistent severe stress incontinence (0-15 %) and erectile dysfunction (29-100%) (13).

Evidence supporting radical prostatectomy as treatment for early PC is based on the well documented Swedish study by Bill-Axelson et al., where 695 men with early PC were randomly assigned to watchful waiting or radical prostatectomy from 1989 to 1999 (14, 15). RP was associated with a reduction in the rate of PC deaths. However, results from recent studies such as the Prostate Cancer Intervention Versus Observation Trial (PIVOT) found no significant differences in mortality between men undergoing surgery for localized PC versus those treated with observation only (16, 17). Persisting uncertainty regarding non-fatal health outcomes and long-term mortality underpins the need for better prognostic markers.

Radical prostatectomy is a well-established and recommended treatment for patients with cT1-cT2 stage cancers, yielding life expectancy of more than 10 years. For cT3 cancers, RP may be performed in selected cases with supplementary regional lymph node dissection. Supplemental adjuvant or salvage radiation and/or hormonal therapy may be needed (18-21). In patients with pT3 tumors and/or positive surgical margin after prostatectomy, adjuvant RT reduces the risk of distant metastasis and leads to better overall survival. An alternative strategy is to provide salvage RT in case of biochemical or local recurrence. Observational studies have shown that up to 50%
of these patients achieve disease control if salvage RT is initiated in early biochemical recurrence (21).

1.6 Radiotherapy
External beam radiotherapy (EBRT) is another option of curative treatment, and functions by damaging the deoxyribonucleic acid (DNA) of malignant cells leading to cell death. Shaped radiation beams are aimed from several angles of exposure to intersect at the tumor, focusing a much larger radiation dose at the malignant target rather than in the surrounding healthy tissue. Intensity modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is considered the best standard for external beam radiotherapy (EBRT) (22). The American Cancer Society found some of the side effects (temporary or chronic) from EBRT of the prostate with margins includes radiation proctitis, radiation cystitis, urine incontinence, urethral stricture, erectile dysfunction, impotence, fatigue and lymphedema (23).

Several randomised controlled trials (RCTs) have shown that dose escalation (range 74-80 Gy) has a significant positive impact on relapse-free five-year survival. The best evidence of an overall survival (OS) benefit for patients with intermediate-risk or high-risk PC, but not with low-risk PC, comes from a retrospective analysis of the U.S. National Cancer Database covering a total of 42 481 patients (24). The Prostate Testing for Cancer and Treatment (PROTECT) study compared active monitoring, radical prostatectomy and external-beam radiotherapy for treatment of clinically localized PC following a PSA testing. At a median of 10 years, PC–specific mortality showed no significant difference among treatments. Surgery and RT were associated with a lower incidence of disease progression and metastases than was active monitoring (13). For low risk disease, single modality EBRT or brachytherapy may be offered. For intermediate risk disease, EBRT or brachytherapy alone or in combination may be offered. In high risk disease, EBRT alone or EBRT combined with brachytherapy with 24-36 months of ADT should be offered.
2 Improving the Oncological Outcomes of Prostate Cancer Treatment with Dose Escalated Radiation Therapy

2.1 Prostate Cancer Dose Escalation using Three-Dimensional Conformal Radiotherapy (3DCRT)

The Patterns of Care study (25, 26) showed that prostate cancer has a radiation dose response i.e. the higher the dose, the greater the probability of cure. However, it also demonstrated an increase in rectal toxicity with older conventional techniques that employed doses greater than 60-64 Gy. Technical improvements in radiotherapy, initially three-dimensional conformal radiotherapy (3DCRT) were developed to reduce the dose to the rectum. 3DCRT can shape beams from multiple angles to match the shape of the tumor. Dearnaley et al. published the first randomised study that illustrated the superiority of 3DCRT when compared to older conventional techniques with significantly less late rectal toxicity when treated to the same dose of 64 Gy (27). The rate of late Grade 1 or greater (G1+) gastrointestinal (GI) toxicity was 37% in the 3DCRT arm compared to 56% in the conventional arm (p=0.004). The rate of late Grade 2 or greater (G2+) GI toxicity was 5% in the 3DCRT arm compared to 15% in the conventional arm (p=0.01).

The use of 3DCRT has led to four RCTs of EBRT (28-31) that showed significantly improved biochemical PSA control rates in men treated in the dose escalated radiation arms. The low dose radiation arms varied in dose from 64-70 Gy while the high dose radiation arms used 74-80 Gy. The median follow-up of these studies was notable varying between five to ten years. All confirmed the advantage of the ‘dose escalated’ high dose radiation therapy (HDRT) in terms of improvement in biochemical PSA control rates with two additional studies also showing a reduction in clinical prostate cancer relapse. However, this did not translate into an overall survival advantage. The standard radiation doses now delivered for prostate cancer range from a minimum of 74 Gy for low risk disease to 78 Gy for intermediate and high-risk disease.

The Radiation Therapy Oncology Group (RTOG) 9406 phase I/II dose escalation study progressively increased the radiation dose delivered to the prostate in 5 incremental dose levels using 3DCRT exclusively (Level I: 68.4 Gy in 1.8 Gy/fraction, Level II: 73.8 Gy in 1.8 Gy/fraction, Level III: 79.2 Gy in 1.8Gy/fraction, Level IV: 74 Gy in 2 Gy/fraction and Level V: 78 Gy in 2 Gy/fraction) (32). The median rectal V70 was 22%. The incidence of late G2+ GI toxicity was 13%, 9%, 14%, 16% and 26% at dose levels I to V, respectively. The incidence of late Grade 3 or greater (G3+) GI toxicity was 6%, 2%, 6%, 9% and 12% at dose levels I to V, respectively. The rates of G2+ GI toxicity are comparable to those reported in the randomised studies. In the MD Anderson trial, the incidence of G2+ GI toxicity was 13% for the 70 Gy arm vs. 26% for the 78
Gy arm. In the Dutch randomised 3DCRT trial, the 5-year late G2+ GI toxicity rate was 27% in the 68 Gy arm compared to 32% in the 78 Gy arm. Similarly, the Medical Research Council (MRC) trial of 64 Gy versus 74 Gy reported 5-year late G2+ GI toxicity rates of 24% for the standard compared to 33% in the dose escalated arms. Notwithstanding the improved radiotherapy technique, dose escalation above 70 Gy also resulted in a near doubling of late GI toxicity as 3DCRT was unable to completely prevent excessive dose to the adjacent rectum. The reported genitourinary (GU) toxicity was similar in both arms.

Viani et al. has performed a meta-analysis of prostate cancer dose escalation in 2009 (33). The study included 7 RCTs using various methods of EBRT (older conventional and 3DCRT), protons and brachytherapy to assess outcomes in men treated with HDRT versus low dose radiation therapy (LDRT). This showed a highly significant reduction in biochemical failure in favour of the HDRT group for all prostate cancer risk groups after a median follow-up of five years. There was a linear relationship between biochemical control and dose i.e. 1.8% for every 1 Gy. However, there was no difference in overall or prostate cancer specific mortality. In addition, there was significantly higher late G2+ GI toxicity after HDRT but no difference in GU side effects.

2.2 Prostate Cancer Dose Escalation using Intensity Modulated Radiation Therapy (IMRT)
IMRT was the next major technical refinement in radiotherapy technique. IMRT uses sophisticated iterative algorithms to substantially modulate/filter the delivered radiation with the motion of tungsten leaves of a multi-leaf collimator. The dose is conformed more intricately to the shape of the target. Notably IMRT, unlike 3DCRT, is able to better conform to the concave shape of the interface between the prostate target and rectum, further minimizing the dose to the rectum.

Randomised control trials have shown that the optimal dose for prostate radiation is at least 74-78Gy and there is evidence that even higher doses may be required for high-risk disease as noted below. There have been numerous planning studies that have shown that IMRT improves the conformity of dose distributions around the Planning Target Volume (PTV) and reduced the rectal doses +/- other organs at risk, when compared with 3DCRT (34-37). Therefore, IMRT appears to be the most appropriate method to deliver these higher doses.

Eade et al. studied a large cohort of 1530 patients with prostate cancer who were treated with 3DCRT (38). The cohort was divided into four dose groups < 70 Gy, 70-74.9 Gy, 75-79.9 Gy and
Radiotherapy dose was found to be significant factor for freedom from biochemical failure. The dose response curves suggested a benefit beyond 80 Gy with a 2.2% gain in long-term freedom from biochemical failure for every 1 Gy. A radiotherapy dose response for distant metastases was also found with an 8% reduction in risk of distant metastases for each 1 Gy delivered. The improved freedom from distant metastases with dose appeared to translate into a survival advantage at 10 years. They concluded that the use of image guidance and IMRT now allows for the delivery of radiotherapy doses of $\geq 80$ Gy with minimal toxicity (29).

The Memorial Sloan Kettering Cancer Centre (MSKCC) executed an extensive serial non-randomised prostate dose escalation program using initially 3DCRT and then IMRT. During their transition from 3DCRT to IMRT, they were one of the first to illustrate the advantages of IMRT. In 2000, Zelefsky et al. reported on a cohort of 332 patients treated to 81 Gy during this transition, 61 patients with 3DCRT and 171 with IMRT (39). They suggest that IMRT may allow for safer dose escalation to doses higher that can be achieved with 3DCRT. IMRT significantly improved the coverage of the CTV whilst significantly reducing the volumes of rectum and bladder cancers that received moderate to high radiation doses. This translated in to a highly significant decrease in rectal bleeding rates. In their experience, the use of IMRT significantly reduced the rate of late G2+ GI toxicity from 13% to 5%. Further analysis showed an improvement in biochemical outcome with increasing dose, notably in the intermediate and groups (40), which translated to a significant decrease in risk of distant metastases (41).

The NRG Oncology RTOG 0126 clinical trial of radiation dose escalation randomised 1532 patients to either 79.2 Gy or 70.2 Gy using 3DCRT or IMRT (42). Approximately 33-34% of patients in both arms received IMRT. The rate of late G2+ GI toxicity was significantly higher in the 79.2 Gy arm compared to the 70.2 Gy arm (21% vs. 15%, p=0.006). A preliminary analysis of toxicity was conducted comparing 3DCRT versus IMRT for the high dose 79.2 Gy arm (43). The median rV70 was 18.2% for the IMRT arm compared to 21.7% for the 3DCRT arm. The rate of acute G2+ GI and/or GU toxicity was 9.7% for the IMRT arm compared to 15.1% for the 3DCRT arm (p=0.042). At 3 years of follow up, the rate of late G2+ GI toxicity was significantly reduced in the IMRT arm compared to the 3DCRT arm (15.1% vs. 22%, p=0.039).

A number of centres are now reporting long-term follow-up, approaching 10 years, of their prostate IMRT patients. The MSKCC have separately analysed and reported on 10-year outcomes in 170 patients treated after high-dose IMRT (81 Gy) (44). The 10-year PSA relapse-free survival
(RFS) rates were 81% for the low-risk group, 78% for the intermediate-risk group, and 62% for the high-risk group. The 10-year distant metastases–free rates were 100%, 94%, and 90%, respectively, and cause-specific mortality rates were 0%, 3%, and 14%, respectively. The 10-year likelihood of developing late Grade 2 and 3 GU toxicities was 11% and 5%, respectively, and the likelihood of developing late Grade 2 and 3 GI toxicities was 2% and 1%, respectively. No Grade 4 toxicity was observed.

Another study with a median follow-up of 10 years was published by Vora et al. and included 302 patients (45). The median dose delivered was 75.6 Gy (range 70.2-77.4 Gy). Local and distant recurrence rates were 5% and 8.6% respectively. The biochemical control rates were 77.4% for low risk, 69.6% for intermediate risk and 53.3% for high-risk disease. At last follow-up, 0% and 0.7% had persistent Grade 3+ GI and GU toxicity respectively. The high-risk group was noted to have a higher rate of distant metastases (39). These findings indicate that IMRT is associated with good long-term prostate cancer control and low rates of serious toxicity in patients with localised prostate cancer.

The use of ultra-high dose IMRT (≥ 86Gy) has also been reported by Deutsch et al. and Petrongari et al. (46, 47). The MSKCC performed a retrospective comparison of biochemical outcomes using ultra high dose IMRT (86.4Gy in 1.8Gy fraction sizes) versus High Dose Rate (HDR) brachytherapy with IMRT (46). The 5-year PSA RFS were 98% vs. 100% (p=0.71) for low, 84% vs. 98% (p<0.001) for intermediate and 71% vs. 93% (p=0.23) for high-risk disease groups, respectively. The 7-year late toxicity rates for Grade 2 GI toxicity were 4.6% vs. 4.1% (p=0.89), for Grade 3 GI toxicity 0.4% vs 1.4% (p=0.36), for Grade 2 GU toxicity 19.4% vs. 21.2% (p=0.14) and Grade 3 GU toxicity 3.1% vs. 1.4% (p=0.74) for ultra-high dose IMRT vs. HDR brachytherapy with IMRT. Petrongari et al. published a prospective phase 2 study that treated 39 intermediate risk prostate cancer patients with ultra-high dose IMRT (86 Gy in 2 Gy fraction sizes) (47). After a median follow up of 71 months, the 5-year freedom from biochemical failure (FFBF) was 87%. The incidence of late G2, G3 and G4 GI toxicity was 18%, 2.5% and 2.5%, respectively. The incidence of late G2 and G3 GU toxicity was 5% and 8%, respectively. However, the use of ultra high dose IMRT is not standard practice with a recent meta-analysis of randomised external beam radiation trials showing no apparent improvement in biochemical control beyond 80 Gy equivalent dose in 2 Gy fractions (48).
While there are numerous single institution studies with the long term follow up of prostate IMRT, there have been no randomized studies of IMRT vs. 3DCRT. The RCTs of prostate dose escalation mainly utilized 3DCRT and illustrated the improved outcome but at the expense of an increase in GI toxicity. The dosimetric planning studies of IMRT vs. 3DCT showed a reduction in rectal doses that translated, in non-randomized studies, to a significant reduction in rectal toxicity. This resulted in a rapid change in equipoise making randomized comparison of 3DCRT vs IMRT unacceptable. An analysis of the SEER database that identified 52290 men with non-metastatic prostate cancer from 2000 to 2007, showed that IMRT had replaced 3DCRT as the primary treatment with external beam radiation (49).

A systematic review comparing IMRT and 3DCRT for prostate cancer was published in 2012 (50). After an extensive literature search they selected 11 articles including 4559 patients, nine retrospective cohort studies and two RCTs (43, 51). The RCTs were randomised studies of dose escalation. Patients were treated with 3DCRT or IMRT, however it was not randomized between the two modalities. The study concluded that there was either, no difference between 3DCRT and IMRT, or as shown in many studies, IMRT had a superior outcome for both acute and late GI and GU toxicity, with a dose escalation of above 70 Gy. They recommended IMRT rather than 3DCRT for radical prostate radiotherapy with doses over 70 Gy. A subsequent economic analysis (based on this systematic review data) demonstrated that for radical radiation treatment (> 70 Gy) of prostate cancer, IMRT appears to be cost-effective when compared with an equivalent dose of 3D-CRT from the perspective of the Canadian health care system for 2009 (52).

The next development in IMRT is volumetric modulated art therapy (VMAT) most often utilizing flattening filter free linear accelerators. Planning studies are increasingly illustrating improved dosimetric quality with improved target coverage and better rectal sparing (53, 54). In addition, the treatment delivery is more efficient and thus treatment time is much shorter (55, 56). This most likely will result in a more precise delivery, as movement is less likely to degrade the delivered dosimetry.

In conclusion, dose escalated IMRT to doses of at least 74-80 Gy has become the EBRT treatment of choice for prostate cancer because large scale studies with long term results have shown that it is at least as effective as 3DCRT, reduces toxicity and is cost effective. In addition, with the rapid development of technology, the planning and delivery, e.g. VMAT, are increasingly quicker and more efficient than older technologies making it possible to deliver even higher doses safely.
However, although we have seen a reduction in late Grade 2+ GI toxicity from 15.1% to 9.7% and in late Grade 2+ GU toxicity from 11% to 5%, further dose escalation with IMRT has seen an increase in both GI and GU toxicity.
2.3 Prostate Cancer Dose Escalation with Hypofractionation

The Linear Quadratic Model with its alpha/beta value describes the curvature of cell killing both for tumour control and normal tissue complications in relationship to radiotherapy dose. The alpha/beta ratio is the dose where the linear as well as the quadratic component cause the same amount of cell killing. Generally speaking, the higher the alpha/beta ratio is, the more linear the cell survival curve is. Whereas the lower the alpha/beta ratio is (high beta relative to alpha), the more curved the cell survival curve is. This is important, as tissues with a low alpha/beta are relatively resistant to low doses, in contrast to tissues with a high alpha/beta. Thus, early responding tissues or rapidly proliferating tumours have a high alpha/beta ratio of more than 10 Gy comparatively late responding tissues or slowly proliferating tumours have a low alpha beta ratio of around 3–5 Gy. Most tumours have a high alpha/beta ratio and can therefore be reasonably treated with conventionally fractionated radiotherapy (using fraction sizes of 1.8 – 2 Gy). But some tumours, i.e. melanoma and sarcoma have a very low alpha/beta ratio and therefore hypofractionation (using fraction sizes >2 Gy) may improve the therapeutic ratio of EBRT (57). It has been suggested that prostate cancer has an alpha/beta ratio of 1.5 Gy, lower than even surrounding tissues such as rectum. In theory, increasing the dose per fraction using hypofractionation may more effectively treat prostate cancer than conventionally fractionated doses (1.8 - 2 Gy) and potentially reduce rectal toxicity.

2.3.1 Moderate Hypofractionation

A growing recognition of the low alpha/beta ratio of prostate cancer has led to several large scale RCTs that demonstrated the non-inferiority of moderate hypofractionation (fraction size 2.4-3.4 Gy) with similar disease control and late toxicity at 5 years. Although different toxicity GI and GU toxicity scales were used (RTOG, EORTC or CTCAE) making comparisons more challenging, we have focussed on grade 2 or more toxicity (requiring medical or surgical intervention) where the definitions are more uniform.

In the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) trial, 3216 patients with predominantly low to intermediate risk prostate cancer were randomised to ADT and IMRT using conventional (74 Gy in 2 Gy) or one of two hypofractionated schedules (60 Gy or 57 Gy in 3 Gy fractions) (58). With a median follow up of 5.2 years, the 60 Gy arm was found to be non-inferior to the 74 Gy arm with respect to biochemical FFS and late toxicity. The estimated 5-year late Grade 2+ GI and GU toxicity was 13.7% and 9.1% in the 74 Gy arm versus 11.9% and 11.7% in the 60 Gy arm. The estimated 5-year late Grade 3+ GI and GU toxicity was 0% and <1% in the 74 Gy arm versus <1% and <1% in the 60 Gy arm.
In the Prostate Fractionated Irradiation Trial (PROFIT), 1206 patients with intermediate risk prostate cancer were randomised to conventional (78 Gy in 2 Gy fractions) or hypofractionated (60 Gy in 3 Gy fractions) IMRT only (59). With a median follow up of 6 years, the 60 Gy arm was non-inferior with respect to biochemical clinical failure disease free survival (DFS) and late toxicity. The late Grade 2 GI and GU toxicity was 11% and 19% in the 78 Gy arm versus 7.4% and 20% in the 60 Gy arm. The late Grade 3 GI and GU toxicity was 2.7% and 2.8% in the 78 Gy arm versus 1.5% and 2% in the 60 Gy arm.

The NRG Oncology 0415 trial randomised 1115 patients with low risk prostate cancer to conventional (73.8 Gy in 1.8 Gy fractions) or hypofractionated (70 Gy in 2.5 Gy fractions) 3DCRT or IMRT (60). With a median follow up of 5.8 years, the 70 Gy arm was non-inferior with respect to biochemical DFS. However, a small statistically significant increase in late Grade 2 GI and GU toxicity was observed in the hypofractionated arm. The estimated 5-year late Grade 2 GI and GU toxicity was 18.3% and 20.5% in the 73.8 Gy arm versus 11.4% and 26.2% in the 70 Gy arm. The estimated 5-year late Grade 3 GI and GU toxicity was 2.4% and 2.1% in the 73.8 Gy arm versus 4.1% and 3.5% in the 70 Gy arm.

In regard to toxicity, the incidence of late Grade 3+ toxicity is low (1-4%) across the three studies at 5 years (58-60). A slight increase in late Grade 2 toxicity was seen in the NRG Oncology 0415 trial. The incidence of GU toxicity may continue to increase between 5 and 10 years. Long term follow up of a phase 2 Princess Margaret Hospital study reported a low 2% cumulative incidence of any Grade 3 toxicity for their hypofractionated 60 Gy cohort. The cumulative incidence of late Grade 2+ GI toxicity was 4% at 5 years and 8 years. The cumulative incidence of late Grade 2+ GU toxicity was 9% at 5 years and 12% at 8 years.

An attempt at dose escalating the hypofractionated arm in the Dutch hypofractionated irradiation for prostate cancer (HYPRO) superiority trial has led to an increase in GI and GU toxicity. In the HYPRO trial, 804 patients with intermediate and high-risk prostate cancer were randomised to conventional (78 Gy in 2 Gy fractions) or dose escalated hypofractionated (64.6 Gy in 3.4 Gy fractions) IMRT (61). After 60 months of follow-up, the 5-year relapse free survival was 77.1% for the conventional arm compared to 80.5% for the dose escalated hypofractionation arm (p=0.36). The 3-year incidence of late Grade 2+ GI and GU toxicity was 17.7% and 39% for the 78 Gy arm compared to 21.9% and 41.3% for the 64.6 Gy arm. Non-inferiority could not be confirmed.
However, cumulative late Grade 3+ GU toxicity was significantly higher in the 64.6 Gy arm (19% vs. 12.9%, \( p=0.021 \)).

Based on the high quality of evidence, moderate hypofractionation should be offered to patients who choose EBRT for treatment of prostate cancer (62). It holds potential advantages for patient convenience and resource utilisation. Moderate hypofractionation (60 Gy) is non-inferior to conventional EBRT (78-80 Gy), however any further attempt at dose escalation has not resulted in improvement of biochemical control, similar late GI toxicity rates but an increase in late severe GU toxicity.

2.3.2 Ultra Hypofractionation
More extreme hypofractionation schedules are currently being explored. Ultra-hypofractionation (fraction size of >5 Gy) is delivered with stereotactic body radiotherapy (SBRT). Multiple single centre prospective studies treating patients with predominantly low risk prostate cancer with SBRT to doses of between 35-36.25 Gy in 7-7.25 Gy fraction sizes have shown excellent biochemical Progression Free Survival (bPFS) of 95-98\% for low risk and 90.7\% for intermediate risk prostate cancer after at least 44 months of follow up (see Table 2) (63-66). The incidence of late Grade 2+ and 3+ GI toxicity ranged from 2-12\% and 0-5\%, respectively. The incidence of late Grade 2+ and 3+ GU toxicity ranged from 4-17\% and 0-2.5\%, respectively. In regard of dose escalation Kim et al. were among the first to undertake a phase I/II dose study of SBRT with 45, 47.5 and 50 Gy in 5 fractions for localized prostate cancer, in which 91 patients were enrolled (67). At the highest dose level of 50 Gy, the incidence of late Grade 2, 3 and 4 toxicities were 24.6\%, 4.9\% and 3.3\%.
2.3.3 Table 2: Prostate Ultra Hypofractionation Results

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Dose/Fraction (Gy)</th>
<th>Median FU</th>
<th>Biochemical PFS</th>
<th>Late G2 Toxicity</th>
<th>Late G3 Toxicity</th>
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<td>35-36.25/7-7.25</td>
<td>60</td>
<td>Low Risk 97% Intermediate Risk 90.7%</td>
<td>2.5%</td>
<td>4.9%</td>
</tr>
<tr>
<td>McBride (57)</td>
<td>45</td>
<td>36.25/7.25</td>
<td>44.5</td>
<td>Low Risk 97.7%</td>
<td>7%</td>
<td>17%</td>
</tr>
<tr>
<td>Freeman (58)</td>
<td>41</td>
<td>35-36.25/7-7.25</td>
<td>60</td>
<td>Low Risk 95%</td>
<td>2.5%</td>
<td>7%</td>
</tr>
<tr>
<td>Loblaw (59)</td>
<td>84</td>
<td>35/7</td>
<td>55</td>
<td>Low Risk 98%</td>
<td>7%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Key: 
N = number of participants; Gy = grey; FU = follow up in months; PFS = Progression Free Survival; G2 = Grade 2; G3 = Grade 3; GI = Gastrointestinal; GU = Genitourinary

The Scandinavian ultra-hypofractionated versus conventionally fractionated RT for PC (HYPO-RT-PC) non-inferiority trial randomised 1,200 patients to conventional IMRT (78 Gy in 2 Gy fractions) or an accelerated hypofractionated SBRT arm of 42.7 Gy in 6.1 Gy fractions reported no difference in late toxicity after 2 years (68). Another ongoing trial is the non-inferiority Prostate Advances in Comparative Evidence (PACE) study that will randomise patients to conventional IMRT (62 Gy in 3.1 Gy fractions) or to a hypofractionated SBRT arm of 36.25Gy in 7.25Gy fractions. To date, the evidence consists of largely prospective single arm trials with limited follow up. No published data from RCTs is currently available. The ASTRO-ASCO-AUA guidelines has given a conditional recommendation for ultra-hypofractionation, reflecting the moderate quality evidence and the remaining uncertainty in the benefit and risk ratio for this treatment strategy (69). The guideline recommended against the use of dose-escalated ultra-hypofractionation beyond 36.25 Gy outside of clinical trials.

2.4 Post-prostatectomy Radiotherapy (PPRT)
The role of dose-escalation and IMRT in the post-prostatectomy setting for PSA salvage is less well documented. Several studies have shown the oncological benefits of dose escalation in PPRT (70-72). In a single institution study in US, Valicenti et al. reported that the 3-year biochemical recurrence free survival was better with PPRT dose of >61.2 Gy in the adjuvant setting (90% vs. 64%), and PPRT dose of >64.8 Gy in the salvage setting (52% vs. 18%) (70). Given the evidence for higher doses in PPRT, multiple national guidelines, including the American Society for Radiation Oncology/ American Urological Association guidelines (73), the German Prostate
Cancer Guidelines (74), and the Australian and New Zealand Radiation Oncology Genito-urinary Group guidelines (75), have all recommended RT doses in the range of at least 64-66 Gy for salvage PPRT versus 60 Gy for adjuvant PPRT.

There is emerging data for even higher doses, with Cozzarini et al. reporting improved 5-year biochemical relapse free survival (83% vs. 71%), and disease-free survival (94% vs. 88%), for dose escalated PPRT to > 70.2 Gy compared to < 70.2 Gy (71). In a systematic review, King et al. reported that the dose response fits a sigmoidal curve for PPRT and parallels that for definitive RT for localised disease, with a dose of 70 Gy achieving 58.6% biochemical Relapse Free Survival (bRFS) vs. 38.5% for 60 Gy (76). The expected proportional gain in bRFS is 2% per incremental Gy. The ongoing phase 3 Swiss Group for Clinical Research 09/10 trial will randomise patients without macroscopic disease to either 64Gy or 70Gy and will help provide further insight into the value of dose escalation (77). In the setting of macroscopic disease, our departmental protocol encourages the use of dose escalated PPRT as recommended by Ost et al. (78) where possible.

However, given the proximity of rectum to the prostatic bed, dose escalation for PPRT can be associated with increased rectal toxicities. When conventional radiotherapy techniques are used, it is estimated that dose-escalation above 72 Gy would result in an unacceptably high rate (20%) of Grade 3 toxicity (79). Whereas, a recent survey among United States physicians revealed that 55% deliver doses of at least 70 Gy and 91% use IMRT (80). A number of studies have concluded that high dose salvage EBRT is safe particularly when IMRT is used and that the 5-year PSA relapse is greater than 70% of patients with pre-treatment PSA <0.5 ng/mL (78, 81). Goenka et al. reported their late Grade 2+ GU and GI toxicities for their IMRT cohort receiving ≥70 Gy at 16.8% and 1.9% (82). Ost et al. delivered far higher PPRT doses with a median of 76 Gy and reported late Grade 2+ GU and GI toxicities at 22% and 8% (78). Ohri et al. reported increased late gastrointestinal toxicity in PPRT by 1.2% per Gray (79).

2.5 Impact of Dose Escalation on Rectal Toxicity
Rectal toxicity has been the dose limiting parameter in prostate cancer dose escalation. The increase in rectal toxicity with dose escalation resulted in more detailed studies that confirmed the dose volume relationship (83, 84). Jackson et al. analysed a subset of 262 patient treated to minimum target doses of 70.2 and 75.6 Gy (83). He classified two groups, patients with Grade 2+ rectal bleeding (bleeders) and patients with Grade ≤1 rectal bleeding (non-bleeders). He analysed the radiotherapy plans and generated average rectal dose volume histograms (DVH) for each
group. He showed that the area under the DVH curve for rectal wall of the bleeders was significantly higher than the non-bleeders. Rectal bleeding correlated with the volume of rectum wall exposed to 46 Gy. There was a borderline significant correlation with the per-cent rectal wall exposed to 71 Gy in the 70.2 Gy group. The results were utilised in the development of their dose escalation studies including IMRT.

Subsequently numerous studies have investigated the dose volume relationship of the organs at risk in prostate radiotherapy. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) (85) is an attempt to summarize available 3D dose-volume/outcome data across a range of normal tissues and organs at risk. For rectal injury they plotted per-cent of rectal volume against linear quadratic equivalent in 2Gy fractions (assuming an alpha/beta ratio of 3) for Grade 2+ late rectal toxicity from the 10 available prostate cancer studies (32). They found that the volume of rectum receiving greater than, or equal to 60Gy, was consistently and significantly associated with Grade 2+ rectal toxicity or rectal bleeding. Whereas rectal volumes receiving less than, or equal to 45 Gy, were not found to be significantly associated with rectal toxicity. Intermediate doses produced mixed results. They also noted that the DVH curves from multiple centres converged at doses >70 Gy and volumes <20%. They recommended dose constraints for the rectum V50Gy<50%, V60Gy<35%, V65Gy<24%, V70Gy<20% and V75Gy<15%. These constraints should limit Grade 2+ late rectal toxicity to <15% and Grade 3+ to < 10% for prescriptions up to 79.2 Gy in standard 1.8-2 Gy fractions. However, they did caution that these have yet to be validated and thus clinicians should always strive to minimize V70 and V75 to below the recommended dose constraints. It was also highlighted that most of the data was from 3DCRT. The use of IMRT has resulted in lower rectal V70 doses than recommended by QUANTEC.

QUANTEC also noted that prostate IMRT often leads to a much lower volume of rectum that receives intermediate to high radiation doses. As intermediate radiation doses are often correlated to the specific 3D techniques used, and the rectal volumes exposed to these doses often correlated to biologically relevant high dose volumes (69). Thus, if intermediate and high dose volumes have biological significance then a reduction of rectal volumes in the 45-60 Gy range by IMRT may become more important as this surrounding rectal tissue may be important for the healing of rectum that receives higher doses.

The QUANTEC study also analysed the bladder dose volume data, the other major organ at risk in prostate radiotherapy (86). However, they did emphasis that there were no studies that
comprehensively reported the 3D bladder dosimetry in relation to toxicity. The vast majority of studies found no dose volume relationship with regard to late GU toxicity and therefore the issue has not been resolved with prostate radiation. Dose constraints have been used for prostate radiotherapy but these are not based on toxicity data but rather used to control and limit the dose in the planning process. As recommended by QUANTEC, clinicians might consider the RTOG 0415 bladder constraints for solid bladder i.e. V>80Gy <25%, V>75Gy <35%, V>65Gy <50%.
3 Brachytherapy

Radiation dose is important. Several randomised clinical trials have demonstrated that a 10 Gy increase in EBRT dose increases the biochemical control rate by about 10% at 5 years (28-31). Even at an EBRT dose of 80 Gy, the biochemical failure rate is still 30%, and the question arises as to whether further dose escalation is of value. The only safe method of further dose escalation is with the use of brachytherapy.

Brachytherapy is high precision, targeted radiotherapy utilising advanced computerised treatment planning and image guided delivery systems to achieve tailored ablative tumour dose to the prostate, whilst sparing the surrounding at risk organs at risk to minimise potential toxicities. The radiation dose to the cancer is much higher than that achievable with any form of EBRT and the rapid fall off in dose outside the prostate spares the adjacent organs from radiation toxicity. It represents the ultimate in dose escalation. Two different brachytherapy techniques can be used to treat prostate cancer: low dose rate (LDR) brachytherapy, in which radioactive seeds are permanently implanted into prostate tissue or HDR brachytherapy, where the radioactive source is temporarily placed into the prostate via implanted catheters. Both types of brachytherapy are safe and effective across a range of clinical presentations of prostate cancer and have been applied relatively consistently. Each may be used as definitive therapy, as is commonly the case for men with more indolent prostate cancer (low risk to favourable intermediate risk prostate cancer), or in combination with an abbreviated course of pelvic EBRT for patients with more aggressive disease (unfavourable intermediate to high risk prostate cancers).

When compared to EBRT, both LDR and HDR brachytherapy have comparable cancer control and long-term survival rates with a reduced risk of side effects. There is no direct clinical evidence that supports the superiority of one modality of brachytherapy over the other, with no prospective randomised comparison available. Brachytherapy also offers significantly reduced overall treatment times compared to EBRT. When combined with lower infrastructure outlay, it is also cost-effective. The advantages of LDR include the use of low energy radiation source such as Iodine 125 (I^{125}) or palladium 103 (Pd^{103}) which means it requires minimal source shielding, can be handled directly by clinical staff and may be placed in a standard operating room. Iridium 192 (Ir^{192}) the most common HDR brachytherapy source, is high energy and requires a shielded room for treatment. Logistically, this necessitates that implants be performed in a shielded operating theatre or if not available, that the implant is left in the patient while they are moved for planning and treatment. This not only increases time demands on radiation oncologists and ancillary clinical
staff but poses workflow challenges regarding anaesthesia and quality assurance steps to minimize the risk of implant displacement. Relative to LDR, HDR brachytherapy offers several advantages as well, with no patient specific radiation precautions required as patients are not radioactive, decreased radiation exposure to clinical staff and general public, increased control over dose delivered and the exploitation of the perceived sensitivity of prostate cancer cells to large individual fraction doses of radiation in contrast to the gradual deposition of dose over many months.

3.1 Low Dose Rate (LDR) Brachytherapy
As a treatment regime, LDR brachytherapy can be performed as a simple outpatient or inpatient procedure in less than an hour, under either regional or general anaesthesia. $^{125}$I emits low energy photons with a limited range in tissue, with most of the dose being absorbed within a few mm of the implanted seeds. A dose of 145 Gy is prescribed as a minimum dose to the prostate and includes a tight 2 to 3mm margin to cover potential extra-prostatic spread. The dose within the prostate is significantly higher, with over one third of the prostate usually receiving a dose higher than 200 Gy. This dose is at least twice that achieved with the most modern of external beam techniques, and explains the high success rate and low nadir PSA values (usually <0.05 ng/mL) achieved with this ablative dose of radiation. A further advantage of brachytherapy is the significant sparing of normal tissue, particularly the rectum and bladder, with a low risk of long-term morbidity or risk of radiation-induced malignancy.

3.2 LDR Monotherapy
Brachytherapy with LDR monotherapy is as effective as EBRT or RP in low to intermediate risk prostate cancer (87). The Prostate Cancer Results Study Group (PCRSG) undertook a comprehensive review of the literature on the efficacy of brachytherapy evaluating more than 50,000 patients with low, intermediate or high-risk disease treated with all available options including EBRT, RP, protons, ADT, HIFU or cryotherapy (87). Studies selected for inclusion in the review had to stratified into recognisable pre-treatment risk groups, have at least 5 years of median follow up and include at least 100 patients for low and intermediate risk disease and 50 patients for high risk disease. In EBRT, patients had to receive at least 72 Gy to the prostate.

Patients with low risk prostate cancer treated with LDR monotherapy had excellent PSA relapse free survival (RFS) sustained with long-term follow up comparable to EBRT and RP including robotic prostatectomy. Many mature series report a disease-free survival of over 90% for men with low and intermediate-risk disease (see Table 3) (88-93). Potters et al. reported long term 12-year bRFS of 89% for low risk patients treated with LDR monotherapy (91). The Seattle Group has
reinforced this result, reporting their long term 15-year bRFS of 86% for low risk patients treated with LDR monotherapy (92). In an Australian study by Wilson et al., the authors reported long-term PSA and toxicity outcomes for patients with localised prostate cancer treated with LDR brachytherapy (93). The 10-year biochemical disease-free survival for the entire cohort was 89%, with Kaplan Meier estimates by pre-treatment risk group to be 96% and 83% for low and intermediate risk disease respectively.

LDR monotherapy is also often used in selected favourable intermediate risk disease with low volume disease (percent cores involved <33%), predominant pattern three histology and one adverse intermediate risk feature. Potters et al. reported long term 12-year bRFS of 78% for intermediate risk patients treated with LDR monotherapy (91). This result has been further reinforced by the Seattle Group, reporting their long term 15-year bRFS of 80% for intermediate risk patients treated with LDR monotherapy (92). The NRG Oncology/RTOG0232 study (94) randomised intermediate risk prostate cancer patients to EBRT (45Gy) and LDR boost (I\textsuperscript{125} or Pd\textsuperscript{103}) versus LDR (I\textsuperscript{125} or Pd\textsuperscript{103}) alone. After a median follow up of 6.7 years, no difference in bPFS has been seen (85% for the EBRT plus LDR-PB boost and 86% for LDR alone). The NRG Oncology/RTOG 0323 study only randomised intermediate risk prostate cancer patients and shed more light on the composition of the intermediate risk groups and its potential impact on bPFS.

3.2.1 Table 3: Long Term Prostate Low Dose Rate Brachytherapy Outcomes

<table>
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</tr>
</tbody>
</table>

**Key:**

\( N = \text{number of participants, FU = follow up} \)

No additional EBRT or ADT is necessary. The latter can be used to downsize the prostate prior to brachytherapy.
Many mature series report a low GU and GI toxicity (see Table 4) (93, 95-98). The incidence of late GU toxicity has significantly declined since the introduction of modern implant techniques such as the modified peripheral implant to spare the urethra. Keyes et al. reported a 10% rate of late Grade 3+ GU toxicity in 2709 patients treated with $^{125}\text{I}$ LDR brachytherapy after a median follow up of 54.5 months (95). Wilson et al. reported a 10.7% rate of late Grade 3+ GU toxicity after a median follow up of 7.8 years (93). As shown in Table 4, the rate of late Grade 2 GI toxicity is between 2.2% to 7.3%, whilst the rate of late Grade 3 GI toxicity is very low, ranging from 0% to 1.1%. The risk of severe GI toxicity is rare with Leong et al. reporting 9 rectal ulcers (0.19%) and 12 rectal fistulas (0.26%) in 4690 patients treated with LDR brachytherapy after a median follow up of 53 months (99). Similarly, Wallner et al. reported 8 rectal fistulas (0.32%) in 2464 patients (100). Although rare, the development of rectal fistulas is often disastrous for the patient involved. The optimal intervention is unclear and a diverting colostomy is typically needed to manage urinary leakage and facilitate spontaneous healing. Surgical repairs of rectal fistulas are largely unsuccessful and major exenterative procedures may be required.

3.2.2 Table 4: Long Term Prostate Low Dose Rate Brachytherapy Toxicity

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Isotope and Dose</th>
<th>Median FU (months)</th>
<th>Grade 2 GI Toxicity</th>
<th>Grade 3 GI Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zelefsky (91)</td>
<td>562</td>
<td>$^{125}\text{I}$ (150 Gy)</td>
<td>40</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Keyes (88)</td>
<td>1006</td>
<td>$^{125}\text{I}$ (150 Gy)</td>
<td>61</td>
<td>7.3%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Wilson (86)</td>
<td>207</td>
<td>$^{125}\text{I}$ (145 Gy)</td>
<td>93.5</td>
<td>2.8%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Shah (89)</td>
<td>135</td>
<td>$^{125}\text{I}$ (145 Gy)</td>
<td>41</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Gomez-Iturriaga Pina (90)</td>
<td>94</td>
<td>$^{125}\text{I}$ (160 Gy)</td>
<td>63</td>
<td>2.2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Key:**

$N = \text{Number of participants, } I = \text{Isotope, } Gy = \text{Gy, } FU = \text{follow up, } GI = \text{Gastrointestinal}$

3.3 LDR in Combination with EBRT

Some brachytherapy centres advocate LDR brachytherapy combined with EBRT to treat patients with unfavourable intermediate risk or high-risk prostate cancer. For intermediate risk disease, the combination of LDR brachytherapy with EBRT appear equivalent to LDR or HDR monotherapy, and appear superior to EBRT (87). In patients with high-risk disease, LDR brachytherapy combined with EBRT and/or ADT is superior to LDR monotherapy, EBRT or RP. The PRSCG
did not find any study that looked at the result of high-risk patients treated with planned surgery and EBRT, so extrapolation for this form of treatment is not possible.

The Seattle Group reported long-term 15-year bPFS of 80% for intermediate risk patients treated with LDR brachytherapy combined with EBRT (101). There is only one randomised study comparing EBRT plus brachytherapy versus brachytherapy alone. The Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) study (102) compared LDR-PB boost versus dose escalated EBRT (78 Gy) with intermediate and high-risk prostate cancer with significant improvement in 7 and 9-year bPFS demonstrated for the LDR brachytherapy arm. This difference was 11% at 7 years (86% vs. 75%), rising to an estimated 21% at 9 years (83% vs. 62%) despite the use of contemporary radiation doses. Even further dose escalation with EBRT may not achieve the outcomes provided by a brachytherapy boost with Spratt et al. (103) reporting inferior 7-year bPFS with EBRT alone to 86.4 Gy versus EBRT plus LDR boost (81.4% versus 92%). Extreme dose escalation beyond 86.4 Gy has proven to be difficult to achieve with normal tissue constraints being the limiting factor.

Although there is a significant difference in bPFS for the ASCENDE-RT study, we are yet to see an improvement in OS. The improvement in bPFS is consistent with an improvement in local control. However, failure of local control can lead to second wave metastases with its effects on quality of life (QoL) and perhaps OS if the patient has an extended life expectancy (104). The ASCENDE-RT study (102) has reported a small improvement in metastatic free survival (MFS) with a difference of 3.8% at 9 years (88.6% versus 84.8%) and 4.9% by actual treatment received (90.1% versus 85.2%). Spratt et al. (103) also found a significant 4.2% improvement in MFS (93% vs. 97.2%, p=0.04). Xie et al. (105) evaluated the surrogacy of MFS for OS for 12,712 patients from 19 randomised trials using individual patient data and found MFS to be a strong surrogate for OS. EBRT alone may not be sufficient treatment as it has a higher risk of bPFS with extended follow up and combined with a longer life expectancy, may likely require more salvage local and/or systemic therapy.

The benefits of dose escalation with a brachytherapy boost can come at a cost with the ASCENDE-RT study (106) reporting markedly increased GU toxicity. The 5-year cumulative incidence of late Grade 3 GU toxicity was 18.4% for LDR-PB arm versus 5.2% for dose escalated EBRT arm (p<0.001). Although the 5-year cumulative incidence of late Grade 3 GI events was higher in the LDR-PB arm (8.1% versus 3.2%), it was not statistically significant. The NRG
Oncology/RTOG 0232 study (94) reported a more modest increase in late Grade 3 GU toxicity (7% for LDR boost versus 3% for LDR alone). The late Grade 3 GI toxicity was no different (3% for LDR boost vs. 2% for LDR alone). Other retrospective LDR boost studies by Yorozu et al. (107) and Spratt et al. (103) reported acceptable rates of late Grade 3 GU toxicity. Yorozu et al. (107) reported a 7-year late Grade 3 GU toxicity of 2% in 1313 men treated with LDR brachytherapy with 48% also receiving EBRT. Spratt et al. (103) found no difference in late Grade 3 GU toxicities with the brachytherapy boost arm when compared to EBRT alone arm (3.1% vs. 1.4% at 7 years, p=0.74).

Although the risk of late Grade 3 GI toxicity is low after LDR brachytherapy, the risk of developing late Grade 2 GI toxicity is still significant when combined with EBRT (see Table 5) (106-111). Serrano et al. in their report of 245 patients treated with LDR brachytherapy of whom 33.5% had supplemental EBRT, the crude rates of late Grade 2+ and Grade 3+ GI toxicity was 6.8% and 2.9% after a median follow up of 7.5 years (111). The risk of Grade 2+ and Grade 3+ GI toxicities were increased 2.8-fold (p=0.002) and 11.9-fold (p=0.003) respectively, if the patient had received supplemental EBRT. Yorozu et al. reported a 7-year late Grade 2+ and Grade 3+ GI toxicity of 7% and 0.3% respectively (107). The rate of Grade 2+ GI toxicity was 12.6% in the combined treatment arm compared to 1.9% in the LDR alone arm (p<0.001). In the ASCENDE-RT study, the 5-year cumulative incidence of late Grade 2 GI toxicity was 31.3% for the LDR-PB arm compared to 20.2% for the dose escalated EBRT arm (106). However, this was not statistically significant (p=0.205). Spratt et al. (103) also found no difference in late Grade 2 or Grade 3 GI toxicity with the brachytherapy boost arm when compared to EBRT alone arm.
3.3.1 Table 5: Long Term Prostate Combined Low Dose Rate Brachytherapy and External Beam Radiation Therapy Toxicity

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>EBRT Dose</th>
<th>% EBRT</th>
<th>Median FU (months)</th>
<th>G2 GI Toxicity</th>
<th>G3 GI Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tran (101)</td>
<td>503</td>
<td>+20-44 Gy</td>
<td>42</td>
<td>24</td>
<td>8.7%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Shiraishi (102)</td>
<td>458</td>
<td>45 Gy</td>
<td>100</td>
<td>45</td>
<td>9.7%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Price (103)</td>
<td>2752</td>
<td>+45 Gy</td>
<td>38</td>
<td>70</td>
<td>6.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Serrano (104)</td>
<td>245</td>
<td>+45-46 Gy</td>
<td>33.5</td>
<td>90</td>
<td>6.8%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Yorozu (100)</td>
<td>1313</td>
<td>+45 Gy</td>
<td>48</td>
<td>67</td>
<td>7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Rodda (99)</td>
<td>188</td>
<td>46 Gy</td>
<td>100</td>
<td>78</td>
<td>31.3%</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

Key: $N =$ number of participants, $EBRT =$ External Beam Radiation Therapy
$Gy =$ Gy, $FU =$ follow up, $G2 =$ Grade 2, $G3 =$ grade 3, $GI =$ Gastrointestinal

3.4 High Dose Rate (HDR) Brachytherapy

HDR is a more recent form of prostate brachytherapy and involves the placement of hollow catheters into the prostate through which a highly radioactive source “steps” under computer guidance. HDR brachytherapy begins with a transrectal ultrasound (TRUS) guided transperineal implant consisting of 15-20 hollow catheters placed symmetrically throughout the prostate, after which image based dosimetric planning will be performed. Dosimetry may be calculated by images acquired directly on the TRUS unit, CT scan or even MRI scan. This allows for great accuracy and precision in treatment delivery, and also easily enables dose delivery outside the prostate. Treatment is delivered in 10 to 15 minutes, and the process of catheter placement and treatment delivery may be performed in under 90 minutes.

3.5 HDR in Combination with EBRT

Two randomised studies have now shown a significant bPFS advantage for HDR brachytherapy plus EBRT over EBRT alone (112, 113). Both studies demonstrated a significant improvement in bPFS for the HDR brachytherapy arms. The 5 year bPFS was improved by 32% (71% vs. 39%) in Sathya et al. (113) and the 7 year bPFS was improved by 18% (66% vs. 48%) in Hoskin et al. (112). Despite the randomised data available, a lack of evidence remains that conclusively supports the benefits of HDR brachytherapy plus EBRT over contemporary, dose escalated EBRT alone. A significant criticism of the randomised trials has been and remains, that EBRT doses employed were lower than current recommended guidelines, with Sathya et al. (113) using 66 Gy and Hoskin
et al. (112) using 55 Gy in their EBRT alone arms. These would now be considered substandard in light of the multiple randomised trials demonstrating biochemical control advantages for EBRT doses of 78-80 Gy. Regardless, both studies significantly improved bPFS for the HDR brachytherapy arms, despite relatively modest HDR boost doses.

Although, no prospective randomised comparisons support a biochemical control improvement for HDR brachytherapy plus EBRT over contemporary dose escalated EBRT, the ASCENDE-RT trial has provided corroborating evidence that adding a brachytherapy boost to pelvic EBRT significantly improved biochemical control compared to men receiving contemporary dose escalated (78 Gy) EBRT for patients with intermediate and high risk prostate cancer (102). The use of EBRT alone resulted in twice as many biochemical failures compared to the LDR brachytherapy plus EBRT arm. However, this improvement in biochemical control came at the cost of increased GU and GI toxicity.

Single institutional experiences have reported good disease control rates comparable to those of the ASCENDE-RT trial with more favourable toxicity profiles (see Table 6) (114-117). The combination of a single HDR treatment and a short course of EBRT can result in a biochemical disease-free survival of over 95%, with a low rate of late toxicity. Galalae et al. combined the results from Seattle, Kiel University and William Beaumont Hospital, reporting 5-year bPFS of 88% and 69% for their intermediate and high-risk patients respectively, treated with HDR brachytherapy boost with EBRT (114). The William Beaumont Hospital reported late Grade 3 GU toxicity of 1% with no late G3 GI toxicity (115). Demanes et al. has reinforced this initial result with their long term 10-year bPFS of 87% and 69% for their intermediate and high-risk patients respectively, treated with HDR brachytherapy boost with EBRT (116). The rate of Grade 3 and Grade 4 GU toxicity was 6.7% and 1% respectively. No Grade 3 or Grade 4 GI toxicity was seen. Yaxley et al. reported a urethral stricture rate of 4.2% after 2005 utilising innovative HDR techniques (117).
The use of HDR brachytherapy with EBRT can lead to an increase in GI toxicity. When HDR is combined with EBRT, the risk of late Grade 3 GI toxicity can be as high as 7%. In the two phase 3 randomised studies comparing HDR with EBRT versus EBRT alone, the risk of late Grade 3 GI toxicity was 3.9% in Sathya et al. and 7% in Hoskin et al. (113, 118). A phase 2 RTOG 0321 study reported a 2.6% combined late Grade 3 GI and GU toxicity (119). A retrospective study by Spratt et al. reported late Grade 2 and 3 GI toxicity of 4.1% and 1.4% respectively for combined brachytherapy and EBRT after a median follow up of 5.3 years (103).

Unlike the proven benefit of ADT with EBRT in management of high-risk prostate cancer, the advantage of neo-adjuvant or adjuvant ADT is controversial when high doses of radiotherapy are delivered to the prostate via brachytherapy (115, 120). The role of ADT has never been tested in a prospective randomised trial for HDR brachytherapy boost patients. However, the current standard practice includes the use of ADT with high-risk HDR brachytherapy boost patients.

3.6 Summary

Brachytherapy is the ultimate form of conformal radiotherapy with reported cancer control rates significantly higher than those associated with EBRT, even when given in doses greater than 80 Gy. Although GI toxicity has been reduced with IMRT, GU toxicity has increased significantly with dose escalation. Unfortunately, the prostatic urethra and part of the membranous urethra (likely responsible for much of the GU toxicity) lie within the PTV. As these structures are difficult to visualise on CBCT, it is still difficult to avoid using IMRT. However, the use of brachytherapy allows for accurate visualisation of the prostatic urethra, permitting for some limitation of dose.
Nevertheless, intense localized delivery of high radiation dose results in some degree of acute urinary toxicity for most men. By avoiding EBRT, the rectal toxicity rate is negligible, and the volume of normal tissue irradiated is far less. This may be a particular concern for younger men, where concern about potential second malignancy induction is greater. There is no evidence that brachytherapy leads to an increased risk of second cancer.

There is a wealth of mature clinical evidence that brachytherapy, either alone or combined with EBRT, results in excellent disease control rates for men with prostate cancer. Results are far superior to those reported with EBRT. In addition, brachytherapy boost with IMRT is also a cost effective treatment compared to IMRT alone (121). Although new EBRT techniques, such as altered fractionation with stereotactic body radiotherapy, are certainly worth investigating, clinical data is very limited. There is no clinical evidence that the results with the newer techniques are superior to that with conventional EBRT. No EBRT technique can deliver radiation with as much precision as brachytherapy, and even the most modern EBRT technique still irradiates a much larger volume of normal tissue. However, the use of brachytherapy which is not unlike surgery, is very much operator dependent and seed or needle insertion can be variable leading to less than ideal dosimetry. This may well explain some of the variation in both GU and GI toxicity reported in the literature.
4 Fiducial Markers

Historically positional verification was based on alignment of pelvic bones, most often on orthogonal images utilizing film. Film verification was time consuming so it was often only done weekly after treatment. The advent of rapid methods of imaging i.e. electronic portal imaging, verification typically is done daily online pre-treatment. However, the prostate can move relative to the pelvic bones and thus this method was considered insufficient for dose escalated IMRT for prostate cancer (122-125). A fiducial marker is an object placed in the field of view of an imaging system which appears in the image produced, for use as a point of reference or measure.

4.1 Prostate and Prostate Bed Motion

A more accurate method of prostate target localization that has rapidly gained acceptance is the use of biologically inert radiopaque fiducial markers. Fiducial markers, first reported by Crook et al., provide a very useful method in localising the prostate during radiotherapy (126). The use of fiducials in the prostate gland is ideal, as they can be implanted with little risk of migration, can easily be visualised in the treatment room and the prostate shape rarely changes significantly during radiation therapy.

Prostate motion can occur between daily radiotherapy treatments, known as intrafractional motion, and even during a radiotherapy fraction, known as interfractional motion. Of the three directional axis, prostate motion is greatest in the anterior-posterior (AP) and superior-inferior (SI) axis, compared to the left-right (LR) axis. An analysis of prostate motion by Schiffner et al. reported interfractional standard deviation of 1-2mm in the LR axis and 2-4mm in both the AP and SI axis (127). In extreme cases, motion can occur up to 7.2mm posteriorly, 9.2mm anteriorly 6.8mm inferiorly and 12.9mm superiorly (128). Intrafractional motion, can range between 0.86-1.8mm in all directional axis and in 14% of fractions, >2mm can occur (129). Prostate motion is secondary to physiological variation in the body such as the bladder volume, rectal distension, levator contractions and even respiration (130).

The success of radiation therapy is based on the accurate delivery of treatment to the target. Daily radiotherapy treatment starts with ensuring the fiducials position is matched with the original position based on the planning CT. The differences in fiducial position are measured prior to radiation delivery, and if necessary, the treatment couch is repositioned, known as ‘couch shift’ to match the intended position. Up to 90% of treatment fractions require such a treatment shift correction when using fiducial localisation (122).
The use of fiducial markers and surgical clips placed in the prostate bed for PPRT is uncommon, but has been reported in the literature (127, 131-139). Reasons for its reported lack of use includes a) the prostate bed is not rigid and therefore fiducial markers cannot completely define the target volume (138), b) the ability to use the existing surgical clips as fiducials (139) and c) availability of alternative localisation techniques such as in room CT used for image guidance radiotherapy known as cone beam computerised tomography (CBCT) (138).

The prostate bed is not rigid and can be divided into two halves, the upper and lower prostate bed. The upper prostate bed can move independently of the lower prostate bed due to the close proximity of the rectum and bladder (133). The lower prostate bed that represents the vesico-urethral anastomosis (VUA) and adjacent peri-urethral tissue is the area at highest risk of recurrence post-prostatectomy and as such needs to be targeted as accurately as possible (140-145). The majority of post-prostatectomy recurrences (70-80%) occur in the lower prostate bed. The upper prostate bed, which represents the posterior bladder wall and seminal vesicle remnant, is at a lower risk of recurrence post-prostatectomy. However, in the era of CBCT, we can identify the upper prostate bed clearly using the bladder/rectum interface, making the use of fiducial markers to delineate the upper prostate bed less relevant. The use of CBCT cannot delineate the VUA or lower prostate bed accurately making the use of fiducial markers pertinent. In addition, the predominant displacement seen in the upper prostate bed is an AP tilt which is very difficult to correct for as most treatment couches do not have the ability to tilt or only possess a limited range to do so (133).

Although surgical clips have the advantage of being non-invasive, some studies have found them difficult to match to because of the varying number and asymmetric shape (136, 137). The use of gold seeds has been found to be reliable as they are easily identifiable, stable and representative of the prostate bed (127, 136, 137).

An analysis of prostate bed motion by Alander et al. who used a combination of gold seed fiducial markers and CBCT reported interfractional standard deviation of 1.4mm in the LR axis, 5.9mm in both the AP and SI axis. Huang et al. who used a combination of surgical clips and CBCT reported interfractional standard deviation of 2.8mm in the LR axis, 3.9mm in the SI axis and 4.3mm in the AP axis. These shifts are similar to that seen for the intact prostate and as such
fiducial markers in the postprostatectomy setting should be given due consideration as we are also moving towards an era of dose escalation in PPRT.

4.2 Fiducial Construction and Design
Fiducials for prostate cancer should be inert, made from easily available material, relatively inexpensive and can be seen for treatment. Typically made from gold, a fiducial marker (or gold seed) is 0.5-1.5mm in diameter, cylindrical in shape and 2-5mm in length. Fiducials undergo a knurling process to add cross cuts to the surface to improve their ‘grip’. Some fiducials have special designs such as a star shaped cross section (Goldlock™, Beampoint, Sweden) and Gold anchors (Naslund Medical AB, Vassvagen, Sweden) fold into a dense marker, all designs to minimise migration. Some markers contain some steel to allow visualisation on MRI (PolyMark™, CIVCO, USA). Some preloaded needles contain two fiducials spaced apart but interconnected by stranded material, to allow deposition into the same lobe with a single pass (Visicoil™, IBA, Germany). Another new fiducial marker is TraceIT, which is a polyethylene glycol (PEG) hydrogel with 1% bound iodine marketed as a soft tissue marker (TraceIT™, Augmenix, USA). It is injected as a particulate injection and is absorbed by the body within 7 months. It is visible on MRI, US, CT and CBCT. In addition, there is no artefact seen on CT. Higher tech fiducials include electromagnetic transponders (Calypso Medical Technologies, Seattle, USA) which transmit radiofrequency waves requires special localisation and tracking system that can track prostate motion during radiotherapy fraction (146). However, Calypso transponders can distort MRI planning images and the system is costly to implement (147). Navotek is a radioactive emitting fiducial but like Calypso, expensive with additional concerns regarding its radioactive seeds.

4.3 Fiducial Numbers and Position
Three fiducial markers are recommended to allow triangulation and measurement of position in different planes (123, 148). Marker loss is uncommon with Deutschmann et al. reporting 1.4% of patients losing one marker during treatment (149). Although three fiducials provide the best alignment, the use of two fiducials when in the apex and base, is nearly as effective as three (127, 148). An example of implanted positions for 3 fiducials for an intact prostate are the right base, left mid zone and right apex, avoiding the urethra. At least 1 cm spacing is desired to allow clear distinction on treatment position verification images. Fiducials are inserted 3-5 mm from the prostate edge and the mid zone fiducial is inserted deeper, to maintain triangulation on a sagittal treatment position verification image.
In the PPRT setting, the lower prostate bed is identified by inserting two to three fiducial markers into the retrovesical tissue just above or at the level of the VUA. The use of two fiducial markers has been found to be effective (127). Although it will not allow us to capture rotational errors, these have been shown to be very small and therefore not expected to contribute significantly to target motion (150).

4.4 Implant Procedure and Complications
According to Shinohara et al. and Linden et al. (151, 152), the insertion of fiducial markers under local or general anaesthesia should be performed at least a few days, preferably one week, before planning CT scan to allow for any oedema or haemorrhage to settle. Patients are recommended to cease their anticoagulant or anti-platelet therapies one week prior to implant, but aspirin can be continued. An empty rectum is required to improve prostate visualisation, and may sometimes require enema insertion prior to the procedure. Igdem et al. assessed pain scores following outpatient TRUS implants without local anaesthesia, reporting low mean pain scores and 87% reported comparable or less pain than the diagnostic biopsy (153).

Patients are positioned in the left lateral or lithotomy position. Lubricant is applied on to the TRUS probe and inserted into the rectum. The prostate should be fully visualised in the axial and sagittal planes for fiducial marker positioning. Once the first position is selected, the needle is inserted through the rectal wall into the prostate. The bevel of the needle must be visualised by observing its proximal and distal end. Once positioned, the stylet is advanced with the deployment of the marker. Another method is using the transperineal approach. The advantage is a lower risk of infection and rectal bleeding with similar risk profile to transperineal biopsies. Moman et al. reported on 914 patients having gold fiducials inserted from 2001. Prior to 2005, 402 patients had fiducials inserted transrectally with two patients developing urosepsis. Since 2005, 512 patients had transperineal implantation without urosepsis (154).

Implantation of fiducial markers in the PPRT setting is best accomplished using the transperineal approach. The patient is set up in the dorsal lithotomy position with a 16F indwelling catheter (IDC) inserted into the bladder. The IDC balloon is filled with 10mls of normal saline. A TRUS probe is then inserted into the rectum to visualise the bladder, urethra and prostate bed. Gentle traction on the IDC balloon seated at the bladder neck would echographically define the anatomy of the VUA. An 18G disposable brachytherapy grid is attached onto the top of the brachytherapy stepper to help guide the injection of tissue fiducial marker (TFM). Using an 18GA needle, a
minimum of two fiducial markers can be inserted on either side of the VUA into the retrovesical tissue.

Severe complications from fiducial insertion are rare. Langenhuijsen et al. reported on complication rates in 209 consecutive patients having four gold fiducials markers inserted transrectally with 6.2% of men reporting moderate complications with pain and fever and 1.9% reporting minor voiding complaints (155). Other minor complications, include haematuria > 3 days, haematospermia (18.5%), and rectal bleeding (9.1%). Igdem et al. reported on 135 patients using a questionnaire following transrectal implantation with 15% describing haematuria, 4% rectal bleeding and 2% fever (153). Contraindications for fiducial markers include allergies to the type of fiducial material to be used (for example gold allergy for gold and iodine allergy for TraceIT).

4.5 Summary
Comparison studies of the use of IGRT/fiducial markers with IMRT versus non-IGRT treatments have generally shown a decrease in late GI and/or GU toxicity (156-158) and in one study there was an improvement in clinical outcome (156). The difference in toxicity can be attributed to the combination of the IMRT technique with reduced dose to organs-at-risk, daily image guidance and margin reduction that IGRT safely permits.
5 Spacers

5.1 Rectal Spacers
Simple measures can be taken to reduce rectal toxicity, including minimising prostate motion as well as educating patients on standardised protocols for rectal/bladder filling prior to each treatment. The use of low residue diet, emptying of rectal gas prior to treatment, enemas and suppositories have shown to reduce prostate motion during radiotherapy (159-161). An endorectal balloon provides a constant rectal volume that can help immobilise the prostate and decrease the amount of rectum irradiated (162). Endorectal balloons have shown to decrease rates of rectal mucosa; changes on proctoscopy and result in less rectal toxicity (163). The anterior rectal wall still remains close to the prostate, and will continue to receive high doses, despite most of the remaining rectum receiving a much lower dose.

In the last few years, the use of devices to reduce radiation doses to the rectum, by displacing the rectum away from the prostate, has gained considerable interest. Prada et al. first described the use of spacer gel in prostate cancer patients, a biodegradable material that temporarily provides separation between the rectum and prostate (164). Spacers are injected into the perirectal space between Denonviller’s fascia anteriorly and the rectal wall posteriorly (165). Apart from integrating spacers into brachytherapy or external beam radiation treatments, other potential roles may allow for a) further dose escalation, b) safer moderate to extreme hypofractionation, c) less dependence on tight safety margins and localisation techniques which are cost and time resource intensive, and d) prostate re-irradiation in the setting of previous pelvic radiation (166).

5.2 Types of Spacers
Spacer materials used in prostate radiation therapy include blood, hyaluronic acid (HA), collagen, polyethylene glycol (PEG) [or more commonly known as hydrogel spacer (HS)] and biodegradable balloons. These should ideally remain stable during treatment and eventually degrade. The ‘blood patch’ technique is the use of patient’s blood as a spacer (167). Crossed linked HA is a naturally occurring polysaccharide found in skin, joints and eyes. Degradation time can take as long as 1 year (164). Synthetic PEG based hydrogels, come prepared in a thin liquid form made from 2 precursors, and when injected, mix and polymerize to expand into a soft hydrogel within 10 seconds. One commercially available system is SpaceOAR™ (Augmenix, Waltham, MA, USA). Compared to HA, hydrogel spacers are cheaper to manufacture, have low allergy and is less viscous with better distribution into the perirectal space (168). They degrade far quicker than HA, with volume stability during a 2 month course of EBRT (169), and is fully absorbed by 6 months,
excreted renally (170). Human collagen, as reported by Noyes et al., is 50% absorbed by 6 months and completely by 12 months (168). Its use is restricted by limited availability and difficulty in attaining correct consistency given the tendency to clump during preparation (171). Another novel spacer is a shaped biodegradable balloon, made from poly (L-lactide-co-caprolactone), first described by Ben-Yosef et al. (172) Once inserted it is inflated with saline and degradation starts at 3 months and is completed usually by 6 months (173).

5.3 Spacer Insertion and Complications
Hatiboglu et al. first described the technique of SpaceOAR™ hydrogel injection, and the technique is essentially no different to the injection of other spacer materials (171). Following bowel and perineal skin preparation, the patient is placed in a lithotomy position and anaesthetised with general anaesthesia, conscious sedation or local anaesthesia. The TRUS probe is inserted to visualise the prostate and rectum interface on both axial and sagittal planes. The 18G needle is inserted transperineally into the perirectal fat, posterior to Denovillier’s fascia and anterior to the rectal wall under TRUS guidance. Hydrodissection is performed, a technique which safely dissects the tissues planes using sterile saline, advancing the bevel to mid gland. The needle is aspirated to ensure it is not within a blood vessel, and 10mls of hydrogel mixture is then injected into this newly created space. The transperineal route is familiar for all urologists, as it is also used for biopsies, fiducial implants, LDR and HDR brachytherapy implants. This procedure is completed within 20 minutes, can be performed under local or general anaesthesia. Antibiotic use is recommended to reduce the chances of infection.

Potential serious complications from spacer injections can include infection, allergic reactions, injection site reactions such as bleeding and pain, urinary retention, rectal pressure, embolization of spacer material and inadvertent injection into the prostate or rectum. So far, published studies have reported no serious adverse events despite initial concerns of potential rectal injury. Spacers however may not be suitable in patients with high risk of adhesions in the perirectal space, including inflammatory bowel disease, chronic prostatitis and perianal disease (174). A review of the Manufacturer and User Facility Device Experience (MAUDE) database for SpaceOAR™ reported 25 cases of major complications (175). However more than 50,000 SpaceOAR™ insertions have been completed thus far, confirming the very rare risk of major complications. As with any invasive procedure, there is always a risk of surgical complications but this can be minimised with appropriate training and mentorship.
5.4 **Spacer Use in Brachytherapy**

Brachytherapy has dosimetric advantages due to the rapid falloff of radiation dose at a distance away from the source. However, rectal toxicity remains a possibility. Rectal dose is a critical parameter to consider as 2-10% of patients undergoing brachytherapy develop rectal complications, ranging from mild proctitis to ulcer and fistula formation (99, 100, 176). To curtail the adverse effects on the rectum, the American Brachytherapy Society guidelines for I\(^{125}\) brachytherapy implant recommend the volume of rectum receiving greater than or equal to the prescription dose (rV100) should not exceed 1cm\(^3\) on day 1 and 1.3cm\(^3\) on day 30.

5.4.1 **HDR Brachytherapy**

Prada et al. originally described the use of HA in 27 men undergoing combined HDR brachytherapy and EBRT (164). Three to seven mls were injected to achieve a mean prostate to rectum separation of 2 cm. The median measured rectal radiation dose was reduced from 47.1% to 39.2%. The mean rectal radiation dose was also reduced by 28% during the HDR brachytherapy boost. No patients had rectal complications.

Wilder et al. reported on 10 patients with HA spacer insertion treated with HDR brachytherapy and IMRT (177). The prostate rectal separation was increased by between 8 to 18mm with concomitant reduction in mean rectal radiation doses. No patients experienced acute diarrhoea (Grade 1-3) compared to a rate of 29.7% in historical controls (p=0.04). A QoL study during radiotherapy in a larger cohort by Wilder et al. showed a larger drop in QOL scores in the 5 patients who had no HA spacer versus the 30 patients who received the HA spacer (178).

Wu et al. reported on 18 patients with 10cc of hydrogel spacer insertion treated with HDR brachytherapy and IMRT (179). HS was successfully injected in all 18 patients. Radiation dose as measured by rectal volume in cubic centimetres was significantly lower for patients with HS insertion compared to a preceding 36 patients without HS.

Yeh et al. reported toxicity outcomes of 326 patients who underwent HDR brachytherapy and IMRT (180). The prostate to rectal separation achieved was 16mm. After a median follow up of 16 months, the incidence of late G1 and G2 toxicities were 12.7% and 1.4% respectively. A follow up study by Prada et al. on 60 patients undergoing HDR monotherapy to 20.5 Gy reported no late Grade 2+ GI toxicity after a median follow up of 51 months (181).
5.4.2 LDR Brachytherapy

Prada et al. first reported on 69 patients treated with LDR brachytherapy, receiving either HA spacer or no spacer (182). In patients with HA spacers, proctoscopic examination showed a lower rate of mucosal damage (5% vs. 36%, p=0.002) and patients reported no rectal bleeding (0% vs. 12%, p=0.04).

The largest study is from the MSKCC where 74 patients had HS insertion following LDR brachytherapy with Pd103 (183). A mean prostate to rectum separation of 11.2mm was achieved. All rectal dosimetric parameters were significantly improved for the cohort with HS insertion when compared to a consecutive cohort of 136 patients without HS.

A prospective study from the Oulu University Hospital in Finland, recently completed their initial pilot of 10 patients injected with Duraseal as a spacer after LDR brachytherapy (184). The mean radiation dose to 2cc volume of rectum was reduced 33% (p=0.005). A follow up study is currently ongoing.

The use of rectal spacers in brachytherapy should be performed after needle insertion to avoid the risk of pubic arch interference. Although the HS is only stable for 3 months before it starts to be absorbed by 6 months, it will provide rectal spacing for at least 2 half-lives for $^{125}$I (59 days) and 6 half-lives for Pd103 (17 days). This means at least 75% of the total dose from $^{125}$I and 99% from Pd103 will be deposited by the time, the HS starts to degrade. The use of HA may be superior for $^{125}$I as it will provide rectal spacing for at least 6 months. However, this is unlikely to affect rectal dosimetry significantly.

5.5 Spacer Use in EBRT
5.5.1 Retrospective and Prospective Phase 2 Studies

Noyes et al. injected 11 patients with human collagen spacer prior to IMRT (168). Hydrodissection was followed by 20mls of human collagen. The mean prostate to rectal separation was 12.7mm with no reported allergic or rectal symptoms. The mean reduction in radiation dose to the anterior wall of rectum was 50%. There was no late rectal toxicity although the duration of follow up is unclear.

Eckert et al. reported on 11 patients undergoing IMRT with the use of HS achieving a mean rectal to prostate separation of 9mm, 14mm and 14mm at the ape, mid zone and base of the prostate respectively (174). At the completion of EBRT, only 5 patients had developed Grade 1 toxicity
with no other severe complications noted. Hydrogel spacer injection was unsuccessful in 1 patient, with failed hydrodissection of the perirectal space, thought to be due to pre-existing adhesions.

Weber et al. demonstrated that even with the most conformal radiotherapy techniques (IMRT, VMAT or proton beam therapy) that better minimise the radiation dose to delivered to the rectum, the use of HS can still reduce the volume of rectum that receives high radiation doses (60-70Gy), with only a slight increase in bladder dose, regardless of radiotherapy technique (185). High doses of radiation to the rectum (>70Gy) has been shown to be predictive for a higher risk of late toxicity (32). The increased bladder dose from spacers is due to anterior prostate displacement but is considered clinically insignificant as prostatic urethral dose is thought to cause persistent GU symptoms rather than bladder dose (86).

Pinkawa et al. assessed the impact of HS on the planning scans of 18 patients (170). All radiation doses to the rectum were significantly reduced by 56% with the use of HS, with the volume of rectum receiving 70 Gy (rV70). The HS also allowed the prostate to be more effectively covered by the intended dose. Of note, the study also reported a learning curve that is inherent in the adoption of any new technique. The mean prostate to rectum separation increased from 11mm to 15mm when comparing their first and second cohort of 32 patients (186). Pinkawa et al. followed 114 patients (54 with hydrogel spacer, 60 without hydrogel spacer) for a median of 63 months following prostate IMRT and published 1.5 and 5-year QOL data changes relative to baseline (187). Increases in mean bowel bother QOL scores (>10 points from baseline) were reported 5 times more often by patients without hydrogel spacer at 1.5 years of follow up (32% vs. 6%, p<0.01). In addition, HS patients had significantly less moderate to severe problems with bowel urgency at 1.5 years (0 vs. 13%, p<0.01) and at 5 years (0 vs. 14%, p=0.01), relative to the patients without hydrogel spacer. Of note, erections sufficient for intercourse at 5 years of follow up were significantly improved in the hydrogel spacer patients (24% vs. 3%, p<0.01) (165).

Song et al. subsequently reported on a multi-centre prospective phase 2 study involving 48 patients where IMRT was used to deliver 78Gy with HS in situ. The patients were scanned with CT/MRI prior to HS insertion, followed by repeat CT/MRI after the procedure. IMRT plans were created in both before/after CT/MRI scans and the dosimetric parameters were compared with one another. The aims of the study were to demonstrate the ability to create a prostate to rectum separation distance of ≥7.5mm at the level of the mid gland and to reduce the rectal V70 by 25% compared to the pre-HS insertion treatment plan. Both end points were successfully achieved. The
use of HS increased the prostate to rectum separation distance by ≥7.5mm (mean 8.1mm) in 95.8% of patients and >25% in rectal V70 was 95.7% of patients (188). Acute Grade 1 and Grade 2 GI toxicity were seen in 39.6% and 12.5% of patients respectively. No patients developed acute Grade 3 or Grade 4 GI toxicity. At 1 year, only 4.3% of patients developed late Grade 1 GI toxicity, with no Grade 2 or greater GI toxicity experienced (189).

5.5.2 Phase 3 Study
The randomised study by Mariados et al. has built upon the initial reports of HS use. This multi-institutional study randomised 222 men with low to intermediate risk prostate cancer to HS or the control arm in a 2:1 ratio. Fiducial markers were placed at the same time for image guidance (190).

The HS was inserted successfully in 99% of patients. The use of HS increased the mean prostate to rectum separation of 1.6±2.2 mm to 12.6±3.9 mm. The median rectal V70 or rV70 (per-cent volume of rectum receiving 70 Gy) was 2.3% vs. 10.5% (78% relative reduction, p<0.0001) in the hydrogel spacer and control arms respectively. No difference in prostate or bladder doses were observed between the arms. Surprisingly, less median penile bulb dose was noted in the hydrogel spacer arm (10.8Gy vs. 21.1Gy, p=0.036). All of the radiation dose plans in the hydrogel spacer arm met all the QUANTEC rectal planning minimal acceptable dose constraints (rV50, rV60, rV65, rV70 and rV75) compared to 92% of the plans in the control arm.

There was no difference in the rates of acute rectal Grade 2 or greater (G2+) toxicity (4.1% vs. 4.2%, p=0.5) or acute G2+ toxicity (37.8% vs. 44.4%, p=0.5) in the hydrogel spacer and control arms. However, patients in the hydrogel spacer arm reported significantly less acute rectal pain (2.7% vs. 11.1%, p=0.22). Haamstra et al. (191) has recently updated the results of the original Mariados study, reporting no change in the 3-year incidence of late Grade 1 or greater (G1+) rectal toxicity in the hydrogel spacer arm of 2% compared to the control arm of 9.2% (p=0.028). The 3-year incidence of late G2+ rectal toxicity in the hydrogel spacer arm was 0% compared to 5.7% in the control arm (p=0.012). In addition, the rate of Grade 1+ urinary incontinence was significantly lower in the hydrogel spacer arm (15% versus 4%).

Radiation therapy induced declines in bowel QOL were similar between both arms at 3 months. However, improved bowel QoL in favour of the HS arm was noted from 6 months onward, becoming significant at 3 years. At 3 years, the mean control bowel QoL score was 5.8 points lower than the HS arm. At 3 years, 41% of control and 14% of HS patients were experiencing
bowel QoL declines beyond the established threshold for minimally important difference (MID 5 points for bowel, p=0.002) (191). Similarly, the radiation therapy declines in urinary QoL was similar between the two arms through to 15 months. At 3 years, the control arm had a 3.9-point decline relative to the HS arm, which was near baseline. Baseline sexual function was low in this study with only 41% reporting a baseline Expanded Prostate Cancer Index Composite (EPIC) sexual score of >60. For those potent at baseline, 37.5% of control and 66.7% of HS patients had retained erections sufficient for intercourse at 3 years. The wellbeing of patients following radiation therapy was also assessed by examining the proportion of number of patients experiencing MID declines in all three QOL domains. At 3 years, 2.5% of patients in the HS arm experienced MID declines in bowel, urinary and sexual QOL compared to 20% of patients in the control arm (191).

5.5.3 Spacer in Hypofractionation
In moderate hypofractionation, late Grade 2+ GI toxicity rates were comparable between three RCTs, ranging from 9-22.4% for hypofractionation (58-60). In addition, there have been multiple trials with at least 44 months of follow up in ultra-hypofractionated SBRT. The rate of late Grade 2+ GI toxicity ranged from 0-12% (63-66). Limiting rectal dose is critical to the safe delivery of ultra-hypofractionation. Alongi et al. published results of a single arm trial of SBRT to 35Gy in 5 fractions (192). Among 40 patients treated, 8 had HS insertion. No late Grade 3+ toxicity was reported after 11 months. In addition, there is also a phase 2 trial to be completed of hypofractionated prostate IMRT to 62 Gy in 3.1 Gy fractions with the use of HA spacer. The primary endpoint is late Grade 2+ GI toxicity. The accrual goal is 36 patients.

5.5.4 Spacer Use in PPRT
There are only two case reports published and a small series of 32 patients reported by Yeh et al. (193) that focus on spacer use in PPRT. Insertion of spacer in post-prostatectomy patients can be challenging, given that the plane for HS insertion is less well-defined following surgery. This is in contrast to spacer insertion in the intact prostate RT setting, whereby there is a well-demarcated prostatic capsule and the spacer is inserted into the potential space immediately posterior to the Denonviller’s fascia. One of the concerns that needs to be taken into consideration during insertion of spacer for PPRT is the possibility of posterior displacement of cancer cells. This may lead to under-treatment of the cancer cells, posterior to the HS, and may therefore compromise on the oncological control. A prerequisite for HS insertion was successful hydrodissection between the local recurrence and rectal wall, as this would have been impossible in the setting of rectal wall cancer infiltration. Hence, it is important that patients are carefully selected to ensure there is
convincing macroscopic local recurrence, and where there is no ambiguity as to whether there is involvement of the anterior rectal wall (194).

Reassuringly, the anterior rectal wall has not been shown to be common site of local recurrence following RP (140-143, 195, 196), which suggest that there is potential role for HS in most patients with macroscopic local recurrence. Earlier studies using transrectal ultrasound guided biopsies to identify the site of biochemical failure following RP showed that the peri-anastomotic site was the most common site of recurrence, with incidence in the range of 60% (140-142). MRI studies among patients with local recurrence also showed that large majority of recurrence sites were peri-anastomotic, retro-vesicle, and seminal vesicle (143, 195, 196).

5.6 Summary
The majority of studies have shown consistent and significant dosimetric rectal sparing effects with the use of spacers resulting in prostate to rectum separation of 12-16mm versus 4-6mm at baseline. In addition, >95% of patients have rectal V70 reductions of at least 15% on their IMRT treatment plans. Benefits of spacer use in brachytherapy patients have also been demonstrated. These effects are associated with observed relative decreases in rectal toxicity. However, despite the use of spacers, image guided localisation of the prostate is still highly recommended. Pinkawa et al. demonstrated prostate motion during a course of EBRT was similar, whether a spacer gel was used or not (169). However, significant posterior displacements (>6.5mm) were reduced with the use of spacers (0% vs. 27%).

The use of rectal spacers also improved GU and sexual function (191). The risk of grade 1 urinary incontinence was significantly reduced and the chances of remaining sexually potent was almost doubled. Although the primary endpoint was reduction in rectal toxicity, its benefits also extended to other OARs, such as the bladder and penile bulb. As such the use of rectal spacers should be considered in all patients undergoing dose escalated radiation therapy. The National Institute for Health and Care Excellence (NICE) in 2017 (197), recommended the use of biodegradable spacers to reduce toxicity during RT by experienced clinicians. This guideline has been followed by Cancer Care Ontario (CCO) in 2019 (198), recommending the use of biodegradable spacers to decrease toxicity and maintain QOL in prostate cancer patients.

An extensive economic evaluation has been performed by Hutchinson et al. (199). The use of a rectal spacer for 3DCRT resulted in a marginal cost increase with a significant reduction in rectal
toxicity assuming rectal toxicity reduction is maintained over 10 years. For high dose SBRT it was immediately cost effective. The threshold values for cost equivalence were $3,040, $7990, $33,000 and $162,000 for grades 1 to 4 rectal toxicity, respectively. Another cost benefit analysis by Levy et al., showed an incremental cost effectiveness ratio of under $10,000 per quality adjusted life year in men with good baseline erectile function in an ambulatory setting (200). These results do contain substantial uncertainty, with more evidence needed to refine future decision making.
6 Outline of the published manuscripts

Following this introduction is a series of published manuscripts grouped into chapters sharing common themes. In addition to the manuscripts each chapter starts with an overview that provides the context for the material that follows, summarizes key findings of the research and discusses developments in the field since the publications. After the presentation of manuscripts in these chapters there is a conclusion that summarizes key findings, and indicates areas for future research.

The use of LDR and HDR brachytherapy has diminished in recent years. However, it remains a potent treatment in patients with prostate cancer encompassing all risk groups. Chapters 7-9 will deal specifically with prostate brachytherapy as a means of prostate cancer radiation dose escalation. Chapter 7 affirms the efficacy of LDR brachytherapy in low and favourable intermediate risk prostate cancer patients. This is an effective method of prostate cancer radiation dose escalation and is used as monotherapy in the above risk groups. A retrospective study of a prospectively collected database of all LDR monotherapy brachytherapy patients treated at Genesis Cancer Care Victoria was undertaken after ethics approval by our institutional review board. This study will review the bRFS and OS achieved in our large patient cohort of almost 400 patients. In addition, this study also contains the largest group of patients having had a prior TURP before completing their LDR brachytherapy. Chapter 8 evaluates the combination of LDR brachytherapy and supplemental EBRT in patients with intermediate risk prostate cancer. The ASCENDE-RT trial demonstrated superior bPFS for the combination of LDR brachytherapy and EBRT over the use of dose escalated contemporary EBRT alone. However, the risk of late Grade 3 GU toxicity was far higher for the combination of LDR brachytherapy and EBRT at 18.4%. A retrospective study of all intermediate risk LDR brachytherapy and EBRT patients treated at Genesis Cancer Care Victoria was undertaken after ethics approval by our institutional review board. This study will review the bRFS and OS in our small patient cohort. In addition, it will also report our late Grade 3 GU toxicity using our contemporary peripheral LDR implant technique. Chapter 9 completes our brachytherapy series of published manuscripts, with the appraisal of the efficacy of HDR brachytherapy and EBRT in intermediate and high-risk prostate cancer patients. Multiple RCTs utilizing HDR and LDR brachytherapy in combination with EBRT has shown its superiority in terms of bRFS over EBRT alone. In this retrospective study, we examined our prospectively collected database of all HDR brachytherapy patients treated at Genesis Cancer Care Victoria after ethics approval by our institutional review board. This study will review the bRFS and OS in our patient cohort of almost 100 patients. It will also report the late GI and GU toxicity when dose escalation with HDR brachytherapy is implemented. In addition, we will also report on
the safety of a small number of patients who had a prior TURP before undertaking combination HDR brachytherapy and EBRT.

The use of IGRT and fiducial markers has revolutionized the delivery of radiation therapy in patients with prostate cancer. Although IGRT can be employed without fiducial markers, the combination of IGRT and fiducial markers with soft tissue analysis is the most effective approach to ensuring accuracy of prostate localization and is now regarded as standard of care at Austin Health and Genesis Care (201). However, its use in post prostatectomy patients is still contentious. The prostate bed is not rigid and like the intact prostate, can move between radiotherapy treatments. As such national guidelines have recommended a safety margin (PTV) that encompasses the prostate bed at risk of recurrence (CTV) by 10mm in all directions to account for this uncertainty. However, this can lead to a significant increase in the volume of normal tissues (bladder and rectum) that is exposed to high dose radiation with consequential increased toxicity. **Chapter 10** deals with the use of tissue fiducial markers that are inserted into the prostate bed at the level of the VUA to improve the accuracy and precision of PPRT. We will evaluate the safety of fiducial markers and the use of IGRT with and without fiducial markers in the day-to-day delivery of PPRT, and how this can impact on the safety margin recommendations. In addition, we will also assess how a small change in safety margin recommendations can impact on the volume of normal tissues (bladder and rectum) that is exposed to high dose radiation.

The use of HS at Genesis Cancer Care Victoria began gradually in early 2013 when 4 patients with recurrent prostate cancer underwent salvage HDR monotherapy having had prior prostate EBRT. The rectum was a significant normal tissue at risk of severe toxicity as a consequence of reirradiation. As such the use of HS was commenced in these 4 patients to expand the peri-rectal space in order to displace the rectum posteriorly. All patients underwent successful HS insertion and no postoperative complications were recorded. In addition, all patients successfully completed their salvage HDR brachytherapy with no late Grade 3 GI toxicities reported. The use of HS was then extended to all prostate cancer patients undergoing HDR brachytherapy and EBRT. **Chapters 11-14** will deal with our use of HS in patients who underwent prostate EBRT with or without HDR brachytherapy boost. **Chapter 11** is an ethics approved prospective phase 2 study designed to evaluate the safety and effectiveness of HS in prostate cancer patients undergoing EBRT. Patients were scanned with CT/MRI prior to HS insertion followed by repeat CT/MRI after the procedure. Treatment plans were created in both before and after CT/MRI scans, and the dosimetric parameters were compared to one another. The safety profile of the HS device, the
prostate to rectal separation distance, its impact on rectal dosimetry and late GI toxicity were assessed. **Chapter 12** expands on the use of HS in prostate cancer patients undergoing EBRT. This is a retrospective study of a prospectively collected database of consecutive prostate cancer patients who underwent HS insertion prior to EBRT. This study was undertaken after ethics approval by our institutional review board. As HS is not clearly visible on CT scans, an MRI scan has been recommended to assist with treatment planning. However, the acquisition of an additional MRI scan (the majority of patients would have had a diagnostic MRI scan) can lead to increased costs and delays in treatment. This study explores the delineation of HS without an MRI scan by varying the CT window levels. This study also will evaluate the effectiveness of HS in patients with large prostate volumes (>100cm³) and those with cT3a disease. In addition, it will also report on the safety, prostate to rectal separation distance, recorded rectal dosimetry compared to historical controls and the incidence of late GI and GU toxicity. **Chapter 13** will specifically report on the use of HS in patients undergoing HDR brachytherapy and EBRT. The safety and effectiveness of HS insertion in patients undergoing HDR catheter insertion and its impact on normal tissue (rectal) dosimetry will be assessed.

As our experience and knowledge of HS has developed, we are now captivated by its potential application in patients undergoing PPRT. **Chapter 14** is a pilot study that explores the use of HS in post-prostatectomy patients who present with unifocal macroscopic recurrences in their prostate bed requiring ultra-high dose salvage PPRT. The use of HS was accepted in this cohort of PPRT patients for the following reasons:

1. Patients who present with a macroscopic recurrence have declared their disease
2. There are only rare reported instances of anterior rectal wall recurrence
3. Prostate bed recurrences are almost always unifocal
4. The recommended RT dose for macroscopic disease is > 72 Gy and preferably 76Gy
5. The risk of late GI toxicity increases with increasing RT dose

This study will assess the safety and feasibility of HS insertion after a radical prostatectomy. In addition, it will assess the impact of HS in reducing normal tissue (rectal) dosimetry, our ability to achieve dose escalation to the macroscopic disease and the impact on acute and late toxicity.
The efficacy of LDR brachytherapy in low to intermediate risk prostate cancer

A single institution analysis of low-dose-rate brachytherapy: 5-year reported survival and late toxicity outcomes

Michael Chao, AFRACMA, FRANZCR1, Sandra Spencer, Dip App Sci Med Rad1, Mario Guerrieri, FRANZCR1, Wei Ding, MD, MSc, Mehran Goharian, BSc, MSc, PhD1, Huong Ho, BSc, MSc1, Michael Nga, FRANZCR1, Danielle Healey, BSc, Grad Dip Coun1, Alwin Tan, MBBS, FRACS1, Chee Chan, MBBS, FRACS, FRCS1, Daryl Lim Joon, MBBS, FRANZCR1, Nathan Lowentschul, MBBS, PhD, FRACS2, Douglas Travis, MBBS, FRACS2, Shomik Sengupta, MS, MD, FRACS3, Yee Chan, FRACS3, Andrew Troy, FRACS3, Trung Pham, MBBS, FRACS3, David Clarke, FRACS4, Peter Lodikas, FRACS5, Damien Bolton, MD, MBBS, BA, FRACS, FRCS3

1Genesis Cancer Care Victoria, Melbourne, Victoria, Australia, Level 5/ 126 Wellington Parade, East Melbourne, Victoria, 3002, Australia, phone: +61 3 8870 3300, fax: +61 3 8870 3388, e-mail: michael.chao@genesiscare.com.au
2The Bays Hospital, Mornington, Victoria, Australia
3Austin Health, Heidelberg, Victoria, Australia
4Western Private Hospital, Footscray, Victoria, Australia
5The Valley Private Hospital, Mulgrave, Victoria, Australia

Abstract

Purpose: To report the 5-year biochemical relapse-free survival (BRFS), overall survival (OS), and long-term toxicity outcomes of patients treated with low-dose-rate (LDR) brachytherapy as monotherapy for low- to intermediate-risk prostate cancer.

Material and methods: Between 2004 and 2011, 371 patients were treated with LDR brachytherapy as monotherapy. Of these, 102 patients (27%) underwent transurethral resection of the prostate (TURP) prior to implantation. Follow-up was performed every 3 months for 12 months, then every 6 months over 4 years and included prostate specific antigen evaluation. The biochemical relapse-free survival (BRFS) was defined according to the Phoenix criteria. Acute and late toxicities were documented using the Common Terminology Criteria for Adverse Events version 4.0. The BRFS and OS estimates were calculated using Kaplan-Meier plots. Univariate and multivariate analyses were performed to evaluate outcomes by pre-treatment clinical prognostic factors and radiation dosimetry.

Results: The median follow-up of all patients was 5.45 years. The 5-year BRFS and OS rates were 95% and 96%, respectively. The BRFS rates for patients with Gleason score (GS) > 7 and GS ≤ 6 were 96% and 91% respectively (p = 0.06). On univariate analysis, T1 and T2 staging, risk-group classification, and prostate volumes had no impact on survival at 5 years (p > 0.1). Late grade 2 and 3 genitourinary (GU) toxicities were observed in 10% and 5% of patients respectively. Additionally, patients with prior TURP had a greater incidence of late grade 2 or 3 urinary retention (p = 0.001). There were 14 deaths in total; however, none were attributed to prostate cancer.

Conclusions: LDR brachytherapy is an effective treatment option in low- to intermediate-risk prostate cancer patients. We observed low biochemical relapse rates and minimal GU toxicities several years after treatment in patients with or without TURP. However, a small risk of urinary retention was observed in some patients.

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Key words: brachytherapy, prostatic neoplasms, transurethral resection of prostate.

Purpose

Low-dose-rate (LDR) brachytherapy has been used in Australia since 1998 as curative treatment, either as a boost to external beam radiotherapy (EBRT) or monotherapy in the management of non-metastatic prostate cancer. More recently, the use of Iodine-125 for permanent LDR brachytherapy implants has gained popularity and received widespread treatment acceptance [1].

Several institutions have reported 5- and 10-year biochemical relapse-free survival ranging from 94-96% [2,3,4] to 87-98.5% [3,5,6,7], respectively. In addition, a number of reviews have demonstrated that LDR brachytherapy is equally effective as EBRT or radical prostatectomy (RP) alone in patients with newly diagnosed low- or intermediate-risk prostate cancer [8,9,10]; however, Rodrigues et al. [9] suggested that large sample size, well designed ran-
domized control trials, and/or prospective comparative studies were needed.

In spite of these positive findings and recommendations for practice, there has been an overall decline in the use of brachytherapy by the medical and radiation oncology communities. There have been a number of explanations put forward including the current emphasis on less aggressive treatment strategies such as active surveillance to the need for experienced personnel and specialized equipment required for potentially successful brachytherapy outcomes [11,12]. Therefore, given its overall decrease in clinical use, the aim of this study was to report on our recent brachytherapy experiences in order to highlight its success as a treatment modality for patients with low- to intermediate-risk prostate cancer, including a cohort which underwent pre-implant trans urethral resection of the prostate (TURP).

Material and methods

Study setting, design, and ethics

This prospective case series assessed the effectiveness and safety of permanent LDR brachytherapy for patients with clinically localized prostate cancer at a private radiation oncology center (Radiation Oncology Victoria) in Melbourne, Australia. Approval for outcome analysis was obtained from the board of Radiation Oncology Victoria. Between 2004 and 2011, 371 patients were treated with 125I brachytherapy as monotherapy. All patients underwent a medical history, physical examination, and serum prostate specific antigen (PSA) level. The T stage was assigned by digital rectal examination, and serum prostate specific antigen (PSA) was assessed. The TPS was upgraded from v. 7.0 to v. 8.0 in 2008. The planning target volume (PTV) was created in 2009, the transition was made to post-implant dosimetry.

Volume study was acquired 2 to 4 weeks prior to implant using a Flex Focus 400 scanner (BK Medical Aps, Denmark) and 8848 biplane transducer. All patients underwent bowel preparation with an aperient. Once under general anesthesia, with the patient in standard lithotomy position, a 16F catheter was inserted to identify urethral position. Transverse images were captured from base to apex in 5 mm intervals, with the urethra standardized aligned to the template along column ‘D’, and imported into the VaritSeed (Varian, Palo Alto, CA) treatment planning system (TPS). Pubic arch extent relative to template coordinates was recorded. Technical feasibility of implant in patients who had undergone prior TURP was assessed. The TPS was upgraded from v. 7.0 to v. 8.0 in 2008. The planning target volume (PTV) was created with a 3 mm expansion anteriorly and 3-5 mm laterally to the prostate as defined on ultrasound. There was no posterior expansion at the interface of the prostate and anterior rectal wall. Urethra and rectum were contoured as organs at risk. Pubic arch extent was contoured on the widest slice, usually mid gland.

Dosimetry was forward planned utilizing TG-43 formulism as described by the American Association of Physicists in Medicine [14] via modified peripheral loading using the following dose goals and constraints: prescription dose of 145 Gy minimum peripheral dose (MPD) to the PTV; dose to 90% of the PTV (D90) > 120%; volume of PTV receiving prescribed dose (V100) > 98%; volume of PTV receiving 150% of prescribed dose (V150) < 65%; volume of PTV receiving 200% of prescribed dose (V200) < 30%; volume of urethra receiving 150% of prescribed dose (V150) < 150% and less than 5%; volume of rectum receiving prescribed dose (V100) < 1.00 cc and less than 5%. Prior to 2009, needles were manually loaded with seeds at standard 1.0 cm spacing. During 2009, the transition was made to pre-loaded, customized needles. Median seed strength was 0.423 mCi (IQR: 0.413-0.433) for the majority of cases. For PTV < 30 cc, median seed strength was 0.306 mCi (IQR: 0.299-0.312 mCi).

Patients underwent bowel preparation prior to implant. Once under general anesthesia, a 16F catheter was inserted and patient position from volume study was reproduced. A check of the prostate and urinary catheter relative to the template was performed. The prostate was stabilized with an empty needle, which was also used to both establish and recheck the zero-retraction plane after implantation of each row. The implant procedure was performed under TRUS and fluoroscopic guidance. Patients were admitted overnight and discharged the following morning after a successful trial of void. Four weeks post-procedure, all patients attended initial follow-up with the treating radiation oncologist and CT for post-implant dosimetry.

Planning and treatment procedure

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**Evaluation of response: clinical endpoints**

Patients were followed up by the radiation oncologist every three to four months after LDR brachytherapy during the first year. Thereafter, all patients were seen every 6 months over the next 5 years. In addition, patients agreed to PSA testing for a minimum of four years, by which biochemical failure was defined using the Phoenix definition of nadir + 2 ng/l following implant and excluding any PSA bounce [15].

Relapse-free survival (RFS) was measured from the date of implant to the date of the first failure of any type (biochemical, clinical, metastases or death due to prostate cancer or treatment); and censored for relapse-free patients at the date of their last PSA test or the close-out date, whichever was earlier. Overall survival (OS) time was measured from the date of implant to the date of death from any cause, and censored for those alive at the date of relapse-free survival.

PSA bounce was defined as a short-term increase of > 0.2 ng/l in PSA, occurring more than 3 months after implant and followed by a spontaneous decline without intervention [16]. The date of the bounce was recorded at the highest PSA value, and the height of the bounce was measured from the lowest PSA value between implant and bounce. Late gastrointestinal (GI) and genitourinary (GU) toxicities reported 90 days after implantation were graded according to the Common Terminology Criteria for Adverse Events v. 4.0 (CTCAE v. 4). The analysis was based on the evaluation of the maximum toxicity score after treatment were presented as mean (plus deviation) or median (interquartile range [IQR]) depending on the underlying distribution of the data. In the case of counts, the crude numbers or percentages were presented. The RFS and OS rates were estimated using the Reverse Kaplan-Meier method. All time to event points were measured from the date or implant to the date of the last PSA test, with censoring considered from the date of relapse.

**Statistical analysis**

Descriptive statistics were calculated to characterize the patient, disease, and treatment features as well as toxicities after treatment were presented as mean (plus deviation) or median (interquartile range [IQR]) depending on the underlying distribution of the data. In the case of counts, the crude numbers or percentages were presented. The RFS and OS rates were estimated using the Reverse Kaplan-Meier method. All time to event points were measured from the date of implant to the date of the last PSA test, with censoring considered from the date of relapse. Survival was measured from the date of implant to the date of last contact, with censoring at the date of death. R statistical software was used for the Kaplan-Meier analyses, whilst StatXact software was used to calculate the 95% confidence interval (95% CI) for PSA response.

**Results**

**Patient characteristics**

Of the 371 patients, 245 (66%) met the low-risk criteria, whilst 122 (33%) had intermediate-risk disease. Median age and PSA value at diagnosis were 67 years (IQR: 42-83 years) and 5.6 ng/ml (IQR: 0.6-15.1 ng/ml), respectively. Median follow-up was 5.45 years with 98%, followed up for at least 4 years. The majority of patients (73%) had a Gleason score of ≤ 6, while 26% had a Gleason score of 7. Of the 102 patients who undertook pre-implant TURP, 97% occurred within three months prior to LDR to manage lower urinary tract symptoms. Table 1 shows the details of the patient characteristics.

**Dosimetry results**

Implant procedure details and the main dosimetric values are reported in Table 2. The mean intraoperative prostate volume was 36.7 cc (IQR: 14.7-64.2 cc). An average of 80 implanted seeds (IQR: 46-119) and 23 needles (IQR: 15-38) were used to attain a median prostate V100 of 123.4% (IQR: 114.3-132.4) and a median prostate V100 of 99.4% (IQR: 96.4-100%). Median rectal RV100 was 0.21 cc (IQR: 0-0.96 cc) and 2.99% (IQR: 0-16.91%). Post-implant dosimetry performed at day 29-30 demonstrated a median prostate Dmax of 99.2% (IQR: 44.3-148%) and a median prostate V100 of 89.5% (IQR: 60.2-99.7%), respectively. Rectal wall was contoured in 92% of patients. Median post-implant rectal RV100 was 0.87 cc (IQR: 0-3.58 cc) and 2.27% (IQR: 0-25.77%) (Table 2).

**Time to relapse-free survival**

The biochemical RFS (BRFS) at 5 years using Kaplan-Meier estimates was 95% (95% CI: 92-97%) for all patients.

---

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Variable</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at implant (years)</td>
<td>67 (42-83)</td>
<td>64</td>
<td>1</td>
</tr>
<tr>
<td>No prior TURP, n = 269</td>
<td>≤ 49</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Prior TURP, n = 102</td>
<td>50-59</td>
<td>59</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>60-69</td>
<td>179</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>70-79</td>
<td>125</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>≥ 80</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>T stage (UICC 7th ed.) at presentation</td>
<td>1c</td>
<td>182</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>2a</td>
<td>126</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>59</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>2c</td>
<td>30</td>
<td>8</td>
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<tr>
<td></td>
<td>Missing</td>
<td>8</td>
<td>2</td>
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<tr>
<td>Gleason score</td>
<td>4</td>
<td>1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>266</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>98</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>PSA at diagnosis [µg/l]</td>
<td>5.6 (0.6-15.1)</td>
<td>92</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>&lt; 4</td>
<td>200</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>&gt; 10</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Risk group (D'Amico classification)</td>
<td>Intermediate</td>
<td>122</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Hormone therapy prior to LDR brachytherapy</td>
<td>No</td>
<td>286</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Yes, ADT</td>
<td>84</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Yes, non-ADT</td>
<td>1</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

*Data presented as median (inter-quartile range [IQR]) or number (percentage)*

ADT – neo-adjuvant hormonal therapy; PSA – prostate-specific antigen; TURP – transurethral resection of the prostate; LDR – low-dose-rate brachytherapy; ADT – adjuvant hormonal therapy
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patients. No difference was observed when stratified according to low (96% vs. 92%; \( p = 0.090 \)). Patients with a Gleason score of 7 had a greater relapse rate than patients with Gleason scores \( \leq 6 \); however, the findings were not statistically significant (\( p = 0.063 \)) (Figure 1).

Similarly, none of the other potential prognostic factors such as pre-implant PSA had a significant effect on time to relapse (all \( p > 0.1 \)). In the 18 patients (5%) with PSA relapse, seven patients have developed local recurrence only, whilst two patients experienced either concurrent nodal relapse or distant metastases. Only one patient developed distant metastases alone. To date, no patient has clinically significant local disease.

**PSA bounce**

A PSA bounce was observed in 137 patients (37%). The median time to developing a bounce was 1.47 years (IQR: 0.34-3.31 years), and the magnitude of the PSA rise during the bounce period was a median of 0.6 ng/ml (IQR: 0.2-6.1 ng/ml). A significantly higher chance of developing a bounce was observed in younger (i.e. \( < 59 \) years of age) rather than older patients (\( p < 0.0001 \)). Other prognostic factors such as T stage, prior hormone therapy, and prostate volume had no significant effect on whether the patient had a PSA bounce (all \( p > 0.4 \)).

**Overall survival**

The overall survival at 5 years according to Kaplan-Meier estimate was 96% (95% CI: 93-98%) for all patients, and was not significant between low 97% (95% CI: 94-98%) and intermediate 94% (95% CI: 88-98%) risk groups (\( p = 0.41 \)). Univariate regression revealed no statistical association for clinical T stage, Gleason scores, by risk group, or prostate volume. There were 14 deaths in total and none were attributed to prostate cancer. Of the 14 deaths, seven deaths were due to other cancers, and seven deaths were due to other causes. The other cancers were: colorectal (\( n = 2 \)) and one each of TCC bladder, non-squamous cell lung, pancreas, leukemia, and lymphoma. The other causes were: cerebrovascular accident (\( n = 2 \)) and one each of acute myocardial infarct, deep vein thrombosis, and ensuing pulmonary embolism, ischemic heart disease, pneumonia, and unknown cause (Figure 2).

### Table 2. Dosimetry findings

<table>
<thead>
<tr>
<th>Dosimetry characteristics</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning target volume (cc)</td>
<td>42.7 (17.7-68.1)</td>
</tr>
<tr>
<td>Number of seeds implanted (n)</td>
<td>80 (46-119)</td>
</tr>
<tr>
<td>Number of needles (n)</td>
<td>23 (15-38)</td>
</tr>
<tr>
<td>Activity (U)</td>
<td>0.54 (0.38-0.58)</td>
</tr>
<tr>
<td>Prostate ( D_{90} ) (%, Gy)</td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>123.4 (114.3-132.4)</td>
</tr>
<tr>
<td>Delivered</td>
<td>99.2 (44.3-148)</td>
</tr>
<tr>
<td>Prostate ( V_{100} ) (%, Gy)</td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>99.4 (96.4-100)</td>
</tr>
<tr>
<td>Delivered</td>
<td>144 (140-145)</td>
</tr>
<tr>
<td>Rectal wall receiving MPD (cc)</td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>0.21 (0-0.96)</td>
</tr>
<tr>
<td>Delivered</td>
<td>0.87 (0-3.58)</td>
</tr>
<tr>
<td>Rectal wall receiving MPD (%)</td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>2.99 (0-16.91)</td>
</tr>
<tr>
<td>Delivered</td>
<td>2.27 (0-25.77)</td>
</tr>
</tbody>
</table>

Data presented as median (inter-quartile range (IQR)) or number (percentage)

ADT – neo-adjuvant hormonal therapy, Gy – Gray, MPD – minimum peripheral dose, \( D_{90} \) – the minimum dose received by 90% of the prostate volume, \( V_{100} \) – the percent volume of the post-implant prostate receiving 100% of the prescribed dose

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![Fig. 1. Time to relapse by Gleason score](image1)

![Fig. 2. Overall survival for all patients](image2)
Late toxicities

Only 6% of patients experienced grade 3 urinary retention symptoms. Patients who underwent a pre-implant TURP were at a higher risk of developing subsequent grade 2 urinary retention toxicities ($p = 0.008$); however, no difference between TURP and non-TURP cohorts was seen in grade 3 urinary retention toxicities. Urinary incontinence requiring pads occurred in three patients (< 1%), whilst grade 3 hematua toxicities occurred in 2% of patients, more common in patients who underwent a pre-implant TURP ($p < 0.001$). No patients including those who had a pre-implant limited TURP developed urethral necrosis or recto-prostatic fistulas. For more detail, see Table 3.

Discussion

The aim of this prospective case series was to report on the safety and effectiveness of LDR brachytherapy for patients with prostate cancer. The results showed our 5-year OS and RFS rates to be 96% and 95% respectively. More so, 80% of patients had reached their PSA nadir at 5-years after implant and only a handful of patients (5%) relapsed within the post-implant follow-up period. In addition, we noted the observed difference between the planned and delivered $D_{90}$ values in our population. At 3-months, 35% of patients had grade 1 toxicities (i.e. hematuria), whilst a small sample of patients (2%) developed grade 3 toxicities. A handful of grade 3 late toxicities were observed with urinary retention (6%), hematuria (2%), and urinary incontinence (< 1%). All other events varied from grade 1 to 2.

Our results were consistent with other international studies, which showed very high local control rates post-LDR brachytherapy. In the study by Peacock et al. [3], 822 patients were treated with LDR brachytherapy alone between 2003-2013. At 5- and 10-years, the biochemical freedom from relapse was 95% and 87%, respectively. In the smaller study by Rea et al. [7], 110 patients ($n = 71$ low-risk; $n = 33$ intermediate-risk) underwent LDR brachytherapy, in which the authors observed the biochemical freedom from relapse rate to be 98.5% in the low-risk group and 81.8% in the intermediate group. In the study by Logghe et al. [17], 274 patients with organ-confined prostate cancer were treated with LDR brachytherapy. Follow-up 5-year data revealed disease-specific survival and overall survival to be 98.5% and 93.5%. Similar to our study numbers, 20 patients developed either local or systemic disease.

Our results were also consistent with other studies in our region. In the study by Millar et al. [18], the authors reported on 382 patients who were treated with permanent implant brachytherapy monotherapy for prostate cancer. At 5- and 8-years, OS was 97% and 94%. In a second study by Wilson et al. [19], the authors reported long-term PSA and toxicity outcomes for patients with localized prostate cancer treated with LDR brachytherapy. More specifically, the 10-year biochemical disease-free survival for the entire cohort was 89%, with Kaplan Meier estimates by pre-treatment risk group to be 96% and 83% for low- and intermediate-risk, respectively.

After brachytherapy, the PSA bounce was observed in 37% of patients almost 18 months after commencement of treatment. In most instances, this ‘spike’ effect was seen in our cohort of younger patients (i.e. < 59 years). Similarly, Kindts et al. [20] noted 70 patients (36%) developing a bounce at 18 months, with a mean magnitude of the PSA rise of 0.67 ng/ml. In addition, the authors observed that younger age and lower treatment activity per volume were significant factors associated with a higher chance of developing a bounce. Both findings reflected recent appropriate criteria for brachytherapy, with consensus views on management strategies as described by the American College of Radiology [21]. In particular, it was reported that PSA bounces were observed in up to 40-50% of all hormone-naive patients, mostly in those patients that were younger, and often 12-30 months after treatment.

In our cohort of 371 patients, which included 102 patients with a prior history of TURP, we were able to demonstrate high local control rates post-brachytherapy. In the study by Prada et al. [6], 57 patients with clinically localized prostate cancer that underwent LDR brachytherapy were followed up for a period of 10 years. Follow-up 5-year data revealed biochemical control, tumor-free survival, and OS were 94%, 96%, and 88%, respectively. In studies by Brousil et al. [22] and Salembier et al. [23], the authors observed that prostate brachytherapy relative to the TURP did not hinder proper dosimetric outcomes or result in significant toxicities. In our study, almost one-third of our population had a TURP prior to brachytherapy, which did not hinder dosimetric outcomes. However, the risk of subsequent grade 2 urinary retention was increased. This was usually managed with short-term intermittent self-catheterization. No patients who underwent a pre-implant TURP developed urethral necrosis or recto-prostatic fistulas.

Table 3. Late toxicities

<table>
<thead>
<tr>
<th>Late toxicities</th>
<th>Grade</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proctitis</td>
<td>1</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>1</td>
<td>1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>&lt; 1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>0</td>
<td>226</td>
<td>86</td>
</tr>
<tr>
<td>(stricture)</td>
<td>1</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>No prior TURP</td>
<td>3</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>0</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>(stricture)</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Prior TURP</td>
<td>3</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0</td>
<td>258</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3</td>
<td>1</td>
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<tr>
<td>No prior TURP</td>
<td>3</td>
<td>1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Hematuria</td>
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<td>90</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Data presented as number (percentage)
TURP = transurethral resection of the prostate.
We were also mindful of the current debate surrounding the relationship between dosimetric criteria and relapse-free survival and/or survival [24] given that our median D90 post-implant was 144 Gy (range, 64-215). However, we observed that other studies reported no statistically significant effect on biochemical disease-free survival or survival when stratified into two (i.e. D90 < 140 Gy and > 140 Gy) or three groups (i.e. D90 ≤ 160 Gy; 160-180 Gy; ≥ 180 Gy). Conversely, Rasmusson et al. [4] found a significant relationship between D90 and biochemical failure-free survival, with 167 Gy considered as the tipping point. However, in our present case series, we did not stratify for arbitrary dose levels.

Given that brachytherapy may cause toxicities as a result of a combination of local trauma and radiation, we were not surprised to confirm examples of long-term GU toxicities (i.e. urinary retention) in 6% of our patients. The rates of late grade 3 GU toxicities found in our analysis were similar to those published in other studies that includ-
ed prostate volumes > 50 cc [25]. However, Millar et al. [18] noted Grade 3 complications (i.e. mostly urinary retention) occurring in only 2.9% of patients. Regardless of these minor rates differences, our findings suggested that implantation of larger glands with seeds was safe in this regard.

Study strengths and limitations

A key strength of our study was that we collected data in a prospective fashion from 571 patients attending a specialist radiation oncology center in Melbourne, Australia. Secondly, feasibility of implant was robustly assessed prior to implant in our TURP cohort, almost one-third of our population. Prior TURP did not hinder dosimetric outcomes or result in significant toxicities. Thirdly, we adhered to the parameters established by the American College of Radiology [2] and the American Brachytherapy Society [26] for transperineal permanent brachytherapy of prostate cancer. Lastly, we reported minimal long-term grade 3 adverse events throughout the 5-year follow-up period. This study also had a series of limitations. In particular, our findings were restricted to a non-randomized and non-blinded approach, which meant it was prone to methodological shortcomings. However, by using this case series design, we demonstrated the overall safety of brachytherapy in patients with prostate cancer. Secondly, our long-term follow-up of patients reported on disease-specific outcomes only. While important, we may have also missed out on understanding the impact of disease on general and disease-specific health-related quality of life.

Conclusions

The results of our prospective case series are in parallel with regionally-based published research that has now provided clinicians with long-term data about the benefit of LDR brachytherapy for patients with clinically localized, low- to intermediate-risk prostate cancer. In particular, these encouraging findings would suggest brachytherapy to be as effective as other radiation and surgical treatment modalities. The observed low to moderate long-term complication rate would suggest that the regime offered in this study was feasible and well tolerated. Our results indicate that a prior limited TURP is not a contraindication for LDR brachytherapy, in which the implant is technically feasible. However, the risk of urinary retention is increased. Further studies using multi-institutional centers, larger sample size, and disease-specific and overall health outcome instruments are needed to clarify the direct impact of brachytherapy on prostate cancer.

Disclosure

The authors report no conflict of interest.

References

Overview

This retrospective study of a prospectively collected database of all LDR brachytherapy patients treated at Genesis Cancer Care Victoria (Radiation Oncology Victoria) was interrogated from 2004 to 2011 to assess the long-term oncological control and toxicity of $^{125}$I monotherapy. There has been a worrying trend in the decline of LDR brachytherapy utilisation in the radiation oncology community for a number of reasons. This has led to a reduction in formal training and overall experience in many centres around the world. The aim of this study was to report the efficacy of LDR brachytherapy alone for patients with low to intermediate risk prostate cancer, including a large cohort who had prior pre LDR brachytherapy TURP.

Of the 371 patients identified, 66% had low risk disease and 33% had intermediate risk disease. The median follow up for all patients was 55 months. The 5-year biochemical RFS for all patients was 95%. The 5-year biochemical RFS for low and intermediate risk disease were 96% and 92% ($p=0.09$), respectively. The 5-year overall survival for all patients was 96%. The 5-year overall survival for low and intermediate risk disease were 97% and 94% ($p=0.41$), respectively.

Late Grade 1 and Grade 2 GI toxicity was seen in 5% and < 1% of patients, respectively. No late Grade 3 GI toxicity was seen. Late Grade 2 and Grade 3 GU toxicity was seen in 9% and 6% of patients, respectively. Patients who had a pre LDR brachytherapy TURP were at a statistically significant increased risk of Grade 2 or greater GU toxicity. The risk of Grade 3 GU toxicity was 9% in the TURP cohort compared to 4% in the non-TURP cohort. However, a TURP was often necessary to relieve obstructive symptoms prior to LDR brachytherapy as a pre-emptive measure to minimise the risk of urinary retention and a subsequent post LDR brachytherapy TURP. The latter would dramatically increase the risk of urinary incontinence.

When compared to the three RCTs that had a conventional dose escalated IMRT arm of at least 74 Gy, the 5-year biochemical control of 95% for LDR brachytherapy in this study was similar to the 85-88% achieved in the RCTs for low to intermediate risk disease. In addition, the risk of late Grade 2 GI toxicity is reduced with LDR brachytherapy compared to IMRT (<1% vs. 11-18.3%). No late Grade 3 toxicity was seen with LDR brachytherapy compared to 0-2.7% for IMRT. Although the risk of late Grade 2 GU toxicity is not dissimilar (9% LDR vs. 9.1-20.5% IMRT), the risk of late Grade 3 GU toxicity is increased with LDR brachytherapy (6% vs. <1-2.8%).
In summary, we have confirmed the efficacy of LDR brachytherapy for low to intermediate risk prostate cancer with excellent long-term biochemical RFS, low risk of GI toxicity and an acceptable risk of GU toxicity.
Combined Low Dose Rate Brachytherapy and External Beam Radiation Therapy for Intermediate-Risk Prostate Cancer

Michael Chao, FRANZCR, Daryl Lim Joon, FRANZCR, Vincent Khoo, FRCSR, Sandra Spencer, Dip App Sc, Huong Ho, B App Sc, M App Sc, Mario Guerrieri, FRANZCR, Farshad Foroudi, FRANZCR, and Damien Bolton, FRACS

ABSTRACT

Introduction: This is a retrospective study conducted to report the tumor control and late toxicity outcomes of patients with intermediate-risk prostate cancer undergoing combination external beam radiation therapy and low dose rate brachytherapy (LDR-PB).

Methods and Materials: Thirty-one patients received 45 Gray (Gy) of external beam radiation therapy to the prostate and seminal vesicles, together with a brachytherapy boost via a transperineal prostate implant of 125I (108 Gy). In addition, some patients received 6 months of androgen deprivation therapy depending on physician preference. Biochemical failure was defined using the Phoenix consensus definition of the nadir PSA +2 ng/mL. Toxicity was graded using the Common Terminology Criteria for Adverse Events version 4.0.

Results: The biochemical progression-free survival, metastases-free survival, and overall survival at 5 years were 87.1%, 96.3%, and 92%, respectively. The incidence of late grade ≥1 and ≥2 genitourinary (GU) toxicities were 54.8% and 6.5%, respectively. The incidence of late grade 3 GU toxicity was 6.5% with urinary retention occurring in two patients requiring either a bladder neck incision or transurethral resection of the prostate. The incidence of late grade ≥1 and 2 gastrointestinal toxicities were 19.4% and 6.5%, respectively. No patients developed grade 3 gastrointestinal toxicity.

Conclusion: Our small series has shown a high biochemical progression-free survival consistent with the ASCENDE-RT and NRG Oncology/RTOG0232 LDR-PB boost arms. In addition, the risk of late grade 3 GU toxicity is far lower than that reported by the ASCENDE-RT study but comparable to other LDR-PB boost and LDR alone reports in the literature. Therefore, we are comfortable to continue offering LDR-PB boost to our patients with intermediate-risk prostate cancer.

RÉSUMÉ

Introduction : Il s’agit d’une étude rétrospective menée pour faire rapport des résultats de contrôle de la tumeur et de toxicité tardive chez les patients présentant un cancer de la prostate à risque intermédiaire et recevant un traitement combiné de radiothérapie par faisceau externe (EBRT) et de curiethérapie adjuvante à faible dose (LDR-PB).

Méthodologie et matériel : 31 patients ont reçu 45 Gray (Gy) de radiothérapie par faisceau externe (EBRT) à la prostate et aux vésicules séminales, avec curiethérapie adjuvante par implant transperinéal 125I (108 Gy) dans la prostate. Certains patients ont également reçu six mois de traitement de privation androgénique, au choix du médecin. La défaillance biochimique était définie en utilisant la définition de consensus de Phoenix de nadir d’APS à +2 ng/mL. La toxicité a été mesurée selon le critère de toxicité CTCAE, version 4.0.

Résultats : Les taux de survie sans progression biochimique (bPFS), de survie sans métastases (MFS) et de survie globale (OS) à 5 ans étaient respectivement de 87,1%, 96,3% et 92%. L’incidence de toxicité génito-urinaire (GU) tardive de grade ≥1 et ≥2 était respectivement de 54,8% et de 6,5%. L’incidence de toxicité GU tardive de grade 3 était de 6,5%, avec, chez deux patients, une incidence de rétention urinaire exigeant soit une incision du col de la vessie (BNI) ou une résection transurinaire de la prostate (TURP). L’incidence de toxicité gastro-intestinale (GI) tardive de grade >1 et 2
Comprehensive Centre Network risk groupings consecutive patients were identified. Intermediate-risk prostate treated with LDR-PB boost. Between 2007 and 2017, 31 a retrospective review of intermediate-risk prostate cancer Patient and Methods study to assess the outcomes of LDR-PB boost in a cohort of ASCENDE-RT study potentially impact on their MFS and/or OS. The combination of external beam radiotherapy (EBRT) with a brachytherapy boost for intermediate- and/or high-risk prostate cancer has shown to be superior to high dose EBRT alone for biochemical progression-free survival (bPFS) [1–3]. In the Androgen suppression combined with elective nodal and dose escalated radiation therapy (ASCENDE-RT) study, patients were randomized to combination EBRT with a low dose rate brachytherapy boost (LDR-PB) vs. dose-escalated EBRT alone. Men randomized to the LDR-PB boost arm were twice as likely to be free of biochemical failure than men who had high dose EBRT alone [1]. However, this improvement in bPFS was offset by a significantly increased risk of late grade 3 genitourinary (GU) toxicity in the LDR-PB boost arm. To date we have not seen an improvement in overall survival (OS) after a median follow-up of 6.5 years. Whether this considerable difference in bPFS (estimated 9-year Kaplan–Meier bPFS 83% for LDR boost vs. 62% for EBRT alone) will translate to an improvement in metastases-free survival (MFS) or OS with extended follow-up is still currently unknown. Fuks et al [4] have hypothesized that local recurrence can lead to a second wave of metastases, which may impact on MFS and eventually OS. This may well have significant consequences for men with a long life expectancy, who choose radiotherapy (RT) as their primary treatment modality. Any discussions involving RT will need to include not only EBRT but also in combination with a brachytherapy boost, as the large difference in bPFS with extended follow-up may potentially impact on their MFS and/or OS. As we begin to deal with the implications of the ASCENDE-RT study [1], we have conducted a retrospective study to assess the outcomes of LDR-PB boost in a cohort of patients with intermediate-risk prostate cancer treated at Radiation Oncology Victoria.

Patient and Methods
Institutional review board approval was obtained to conduct a retrospective review of intermediate-risk prostate cancer treated with LDR-PB boost. Between 2007 and 2017, 31 consecutive patients were identified. Intermediate-risk prostate cancer disease was defined according to the current National Comprehensive Centre Network risk groupings [5]. Patients were further subdivided into an unfavourable intermediate-risk group if patients had International Society of Urological Pathologist (ISUP) grade 3 prostate cancer or if they had ISUP grade 2 prostate cancer with cT2c or a PSA between 10–20. These men received EBRT to the prostate and seminal vesicles and a permanent 125I brachytherapy implant. Some patients received 6 months of androgen deprivation therapy depending on the patient’s physician preference.

Treatment
The EBRT was delivered to the prostate and seminal vesicles with either three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT) to a dose of 45 Gy in 25 fractions using 1.8 Gy fractions. Fiducial markers were inserted in 66% (n = 21) of patients for image-guided radiotherapy (IGRT). In the absence of fiducial markers in situ, bony matching was used for IGRT. All patients with fiducial markers had IMRT. The clinical target volume (CTV) was defined as the prostate and seminal vesicles. A planning target volume (PTV) was created with a 7 mm margin all around the CTV except posteriorly where the expansion was limited to 5 mm with fiducial marker verification. In the initial cohort of patients undergoing bone matching for IGRT, the PTV was a 10 mm margin all around the CTV except posteriorly where it was limited to 7 mm. Departmental bladder and rectal filling protocols were followed. Dosimetry was forward planned for 3DCRT and inverse planned for IMRT on the Pinnacle v6–8 (Philips, Fitchburg, WI) treatment planning system. For 81% patients (n = 25), LDR brachytherapy was performed 2–4 weeks after the completion of EBRT. The remaining 19% of patients (n = 6) underwent LDR brachytherapy before EBRT because of social reasons. In all patients, the LDR implant was performed by interstitial implantation using a transperineal template technique under transrectal ultrasound guidance. Volume study was acquired 2 weeks before the implant for preplanning. The brachytherapy CTV was the prostate alone identified on the transrectal ultrasound. PTV was generated with a 3 mm expansion all around except posteriorly at the prostate/rectal wall interface, where no margin was applied. Dosimetry was forward planned adhering to TG-43 formulation in the Variseed v8.0 (Varian, Palo Alto, CA) treatment planning system. Prescribed dose was 108 Gy for 125I. Median seed strength was 0.43 mCi (IQR 0.413–0.433). A computed tomography scan was obtained 4 weeks post implant to assess dosimetry.

Statistics
The database was closed for analysis in December 2017. Biochemical failure was defined using the Phoenix consensus...
definition of the nadir PSA +2 ng/mL. Confirmation of local recurrence or distant metastases was based on radiographic or biopsy findings. Toxicity was graded using the Common Terminology Criteria for Adverse Events version 4.0.

Five-year product-limit estimates (Kaplan–Meier method) were calculated for the following prognostic factors: cT stage, ISUP grading, % biopsy core positive, risk group, and androgen deprivation therapy for different end points (bPFS/MFS/OS). The log-rank test was used to determine the magnitude of difference between the prognostic factors.

### Results

The median follow-up for the entire group was 62 months (7–125 months). The clinical characteristics of the patients are listed in Table 1. Median age was 71 years (51–83 years). Median PSA was 6.7 ng/mL (1.9–9.9). Mean and median dose received by 90% of the prostate (D90) were 100.1% ± 4.7 and 99.6% of the prescribed dose (108 Gy), respectively. Mean and median percentages of prostate volume receiving 100% of the prescription dose (V100) were 87.7% ± 3.4 and 89.7%, respectively.

The bPFS, local recurrence-free survival, and metastases-free survival (MFS) at 5 years were 87.1%, 95.5%, and 96.3%, respectively. The prostate cancer-specific survival and OS at 5 years were 100% and 92%, respectively. As shown in Table 2, we were unable to establish any predictors of bPFS, MFS, or OS on univariate analysis. Four patients had biochemical recurrence occurring at 24, 42, 58, and 104 months after initial presentation. Two patients had seminal vesicle recurrences detected on prostate-specific membrane antigen positron emission tomographic scans when their biochemical recurrence was confirmed (58 and 104 months). One patient had an oligometastasis detected on his prostate-specific membrane antigen positron emission tomographic scan 10 months after his biochemical recurrence (24 months) and subsequently had stereotactic body radiotherapy directed at the oligometastasis. The final patient has not developed any detectable local recurrence or metastases 73 months after his biochemical recurrence (42 months).

The incidence of late grade ≥1 and ≥2 GU toxicities were 54.8% and 6.5%, respectively. The most common late grade 1 toxicities were urinary urgency, urinary tract pain, urinary retention, and urinary frequency. The incidence of late grade 3 GU toxicity was 6.5% with urinary retention occurring in two patients requiring either a bladder neck incision (BNI) or transurethral resection of the prostate (TURP). Of the four patients who had BNI or TURP before their treatment, one patient who had a prior BNI developed further retention with urethral stricture and required a subsequent TURP. The incidence of any late GU toxicity was 80% in the 3DCRT with bone matching IGRT cohort vs. 43% in the IMRT with fiducial marker cohort.

The incidence of late grade ≥1 and 2 gastrointestinal (GI) toxicities were 19.4% and 6.5%, respectively. The grade 2 toxicities were rectal bleeding and radiation proctitis. No patients developed grade 3 GI toxicity. There was no difference in late GI toxicity with two grade ≥1 toxicity (20%) reported in the 3DCRT with bone matching IGRT cohort vs. five grade ≥1 toxicity (24%) in the IMRT with fiducial marker IGRT cohort.

### Discussion

Three randomized studies have now shown a significant bPFS advantage for brachytherapy plus EBRT over EBRT alone [1–3]. Two older studies employed high dose rate (HDR) brachytherapy boosts with Iridium 192 implants plus EBRT vs. nondose-escalated EBRT alone(2, 3). Both studies demonstrated a significant improvement in bPFS for the brachytherapy arms. The 5-year bPFS was improved by 32% (71% vs. 39%) in Sathya et al [2], and the 7-year bPFS was improved by 18% (66% vs. 48%) in Hoskin et al [3]. However, the EBRT doses employed were lower than current recommended guidelines, with Sathya et al [2]

| Table 2 | Univariate Analysis of Clinical Factors That May Influence bPFS, MFS, and OS |
|----------|-----------------|-----------------|-----------------|
| **Clinical Prognostic Factors** | **bPFS (P Value)** | **MFS (P Value)** | **OS (P Value)** |
| cT Stage (T1 vs. T2) | .14 | .4 | .22 |
| ISUP Grade 1 vs. 2 and 3 | .67 | .78 | .73 |
| ISUP Grade 2 vs. 3 | .94 | .44 | .06 |
| % Core Positive (<50% vs. ≥50%) | .14 | .37 | .21 |
| Intermediate-Risk Group (Favourable vs. Unfavourable) | .82 | .55 | .44 |
| ADT (Yes or No) | .08 | .72 | .58 |

bPFS, biochemical progression-free survival; MFS, metastases-free survival; OS, overall survival; cT, clinical tumor; ISUP, International Society for Urological Pathology; ADT, androgen deprivation therapy.
using 66 Gy and Hoskin et al [3] using 55 Gy in their EBRT alone arms. The ASCENDE-RT study [1] compared LDR-PB boost vs. dose-escalated EBRT (78 Gy) with significant improvement in 7 and 9 year bPFS demonstrated for the brachytherapy arm. This difference was 11% at 7 years (86% vs. 75%), rising to an estimated 21% at 9 years (83% vs. 62%) despite the use of contemporary radiation doses. Even further dose escalation with EBRT may not achieve the outcomes provided by a brachytherapy boost with Spratt et al [6] reporting inferior 7 year bPFS with EBRT alone to 86.4 Gy vs. EBRT plus LDR boost (81.4% vs. 92%). Extreme dose escalation beyond 86.4 Gy has proven to be difficult to achieve with normal tissue constraints being the limiting factor. There is only one randomized study comparing EBRT plus brachytherapy vs. brachytherapy alone. The NRG Oncology/RTOG0232 study [7] randomized intermediate-risk prostate cancer patients to EBRT (45 Gy) and LDR boost (1125 or Pd103) vs. LDR (1125 or Pd103) alone. After a median follow-up of 6.7 years, no difference in bPFS has been seen (85% for the EBRT plus LDR-PB boost and 86% for LDR alone).

The bPFS of our small retrospective cohort of intermediate-risk prostate cancer patients is 87.1% at 5 years, consistent with the intermediate risk cohort of patients in the ASCENDE-RT study of 86% at 7 years and the NRG Oncology/RTOG0232 study [7] of 85% at 5 years. This is only marginally inferior to the bPFS of 92% achieved in our LDR brachytherapy-alone cohort of favourable intermediate-risk patients with Gleason 7 disease [8]. This cohort consisted of Gleason score 3+4=7 or ISUP group 2 prostate cancers with PSA <10 and clinical stage T1c-2a disease only. In addition, the percentage biopsy core positive rate was lower (72% had <50% cores positive). On the other hand, this study consisted of patients with predominantly unfavourable intermediate-risk disease. In addition, patients with favourable intermediate-risk disease had a higher percentage core biopsy positive rate (55%>50% core positive). This is likely to account for the lower bPFS. However, our univariate analysis has not shown any statistically significant difference in bPFS between Gleason 3+4=7 (ISUP group 2) vs. Gleason 4+3=7 (ISUP group 3), percentage core biopsies positive of <50% vs. >50% or for favourable vs. unfavourable intermediate-risk disease. It is acknowledged our study is likely too small to reveal a statistically relevant difference. The NRG Oncology/RTOG 0323 study only randomized intermediate-risk prostate cancer patients, and we eagerly await its final publication, which may shed more light on the composition of the intermediate-risk groups and its potential impact on bPFS.

No intraprostatic recurrence has so far been detected in the four patients with biochemical recurrence. Two patients had seminal vesicle recurrence, both with identical clinical characteristics of clinical stage T2a, PSA <10, and G3+4=7 prostate cancers; however, both had ≥50% core positive disease.

Although there is a significant difference in bPFS as reported in the three randomized studies, we are yet to see an improvement in OS [1–3]. The improvement in bPFS is consistent with an improvement in local control. However, failure of local control can lead to a second wave of metastases with its effects on quality of life and perhaps OS if the patient has an extended life expectancy [4]. The ASCENDE-RT study [1] has reported a small improvement in MFS with a difference of 3.8% at 9 years (88.6% vs. 84.8%) and 4.9% by actual treatment received (90.1% vs. 85.2%). Spratt et al [6] also found a significant 4.2% improvement in MFS (93% vs. 97.2%, P = .04). Xie et al [9] evaluated the surrogate of MFS for OS for 12,712 patients from 19 randomized trials using individual patient data and found MFS to be a strong surrogate for OS. This may well have major implications for younger men who choose to have radiotherapy for their localised prostate cancer and the radiation oncologists managing them. EBRT alone may not be sufficient treatment as it has a higher risk of bPFS with extended follow-up and combined with a longer life expectancy, may likely require more salvage local and/or systemic therapy. As such, a discussion regarding combination therapy with a brachytherapy boost is likely necessary. Of course, this will need to be in the context of a potential increase in GU toxicity.

The benefits of dose escalation with a brachytherapy boost can come at a cost with the ASCENDE-RT study [10] reporting markedly increased GU toxicity. The 5-year cumulative incidence of grade 3 GU toxicity using the modified LENT-SOMA scale was 18.4% for LDR-PB arm vs. 5.2% for dose-escalated EBRT arm (P < .001). Although the 5-year cumulative incidence of grade 3 GI events was higher in the LDR-PB arm (8.1% vs. 3.2%), it was not statistically significant. The NRG Oncology/RTOG0232 study [7] reported a more modest increase in late grade 3 GU toxicity (7% for LDR boost vs. 3% for LDR alone). The late grade 3 GI toxicity was no different (3% for LDR boost vs. 2% for LDR alone). Other retrospective LDR boost studies by Yorozu et al [11] and Spratt et al [6] reported acceptable levels of late grade 3 GU as well as GI toxicity. Yorozu et al [11] reported the outcomes of 1313 men treated with LDR brachytherapy with 48% also receiving EBRT with the 7-year late grade 3 GU and GI toxicity at 2% and 0.3%, respectively. Spratt et al [6] found no difference in late grade 3 GU toxicity with the brachytherapy boost arm when compared to EBRT-alone arm (3.1% vs. 1.4% at 7 years, P = .74). The late grade 3 GI toxicity was also no different (0.4% vs. 1.4% at 7 years, P = .36). The HDR randomized studies found no statistically significant difference in late grade 3 GU or GI toxicity [2,3]. A phase 2 RTOG 0321 study [12] reported a 2.6% combined late grade 3 GU/GI toxicity. In this study, the cumulative incidence of late grade 3 GU toxicity was 6.5%, consistent with most reports except the ASCENDE-RT study [10]. This is no different to the incidence of late grade 3 GU toxicity in LDR alone and this is widely considered to be acceptable [8,13–15].

There are a number of limitations in this study, which includes the small number of patients, the time span of the study, and the different IGRT and EBRT techniques
(3DCRT vs. IMRT) but our brachytherapy technique and dose prescription remained unchanged. Of note, our late GI toxicity rates were similar when comparing the 3DCRT vs. the IMRT cohort. This is where the difference in EBRT technique may have had an impact with wider PTV margins mandated for 3DCRT with bone-matching IGRT. However, this is likely to have been minimal because of the low dose delivered (45 Gy). The overall late GU toxicity rates were unexpectedly different with a cumulative incidence of 80% for the 3DCRT vs. 43% for the IMRT cohort. The technical heterogeneity may account for this clinical difference but the small 3DCRT cohort is likely to exaggerate the difference.

Conclusion

In conclusion, our small series has shown an acceptable bPFS and low risk of late grade 3 GU toxicity consistent with other reports in the literature. The large difference in bPFS observed in the ASCENDE-RT study in favour of the LDR-PB boost arm compared to contemporary dose-escalated EBRT alone arm has the potential to impact on quality of life, whereas the small improvement in MFs may potentially impact on OS if life expectancy is prolonged. Younger patients with intermediate-risk prostate cancer will expect radiotherapy consultations that include not only a discussion of EBRT alone, but in combination with a brachytherapy boost, or perhaps brachytherapy alone. This will need to be balanced against the potential of increased GU toxicity.

Footnotes

Contributors: All authors contributed to the conception or design of the work, the acquisition, analysis, or interpretation of the data. All authors were involved in drafting and commenting on the paper and have approved the final version.

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Competing interests: All authors declare: no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval: Institutional review board approval was obtained to conduct a retrospective review of intermediate-risk prostate cancer treated with LDR-PB boost.

References


Overview
This retrospective study of a prospectively collected database of all LDR brachytherapy patients treated at Genesis Cancer Care Victoria (Radiation Oncology Victoria) was interrogated from 2004 to 2017 to assess the long-term oncological control and toxicity of combined EBRT and LDR brachytherapy boost (EBRT-LDR boost). The ASCENDE-RT trial reported superior biochemical PFS for EBRT-LDR boost compared to dose escalated EBRT alone. Patients who were randomised to EBRT-LDR boost were twice as likely to be free from biochemical failure than men who had EBRT alone. The estimated 9-year Kaplan Meier biochemical PFS was 83% for EBRT-LDR boost vs. 62% for EBRT alone. However, the risk of late Grade 3 GU toxicity was significantly increased in the EBRT-LDR boost arm. The aim of this study was to report the efficacy of EBRT-LDR boost for patients with intermediate risk prostate cancer, in particular the risk of late GU toxicity.

Thirty-one intermediate risk prostate cancer patients were identified. The median follow up for all patients was 62 months. The 5-year biochemical PFS for all patients was 87.1%. The 5-year overall survival for all patients was 92%. The incidence of late Grade 2 GI toxicity was 6.5%. No patients developed late Grade 3 GI toxicity. The incidence of late Grade 3 GU toxicity was 6.5%, far lower than that reported in the ASCENDE-RT EBRT-LDR boost arm of 18.4% and similar to the EBRT alone arm of 5.2%. Our late Grade 3 GU toxicity rate is no different to that reported in other phase 3 randomised, phase 2 prospective and retrospective studies. We adhered to strict LDR planning protocols where a modified peripheral implant was used to minimise the radiation dose to the prostatic urethra. In the ASCENDE-RT trial, a uniform prostatic implant was predominantly utilised with consequential higher prostatic urethral radiation dose exposure.

In summary, we have confirmed the efficacy of EBRT-LDR boost for intermediate risk prostate cancer with excellent long-term biochemical PFS and an acceptable risk of late GI and GU toxicity. The risk of late Grade 3 GU toxicity is not significantly higher than that reported for LDR monotherapy in the hands of experienced LDR brachytherapists using contemporary LDR brachytherapy protocols and techniques. However, the long-term biochemical control rates can be substantially improved with the use of EBRT-LDR boost.
The efficacy of HDR brachytherapy and EBRT in intermediate to high risk prostate cancer.

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

Michael Chao,1,2,3,4 Damien Bolton,2,3,4 Daryl Lim Jooin,2 Yee Chan,2,3 Nathan Lawrentschuk,2,4 Huong Ho,1 Sandra Spencer,1 Jason Wasiak,2,4 Mario Guerrieri,2 Darren Ow,2 Andrew Troy,2,3 Trung Pham,8 Shomik Sengupta,8 Alwin Tan,7 Kevin McMillan,3,6 George Koufogiannis,3 Farshad Foroudi,2,3 9 Michael Ng1 and Vincent Khoo2,3,8,9

1 Gemanic Cancer Care Victoria, Ringwood, Australia
2 The Austin Hospital, Heidelberg, Australia
3 Ringwood Private Hospital, Melbourne, Victoria, Australia
4 University of Melbourne, Melbourne, Victoria, Australia
5 The Valley Private Hospital, Melbourne, Victoria, Australia
6 The Geelong Hospital, Melbourne, Victoria, Australia
7 The Royal Melbourne Hospital, Melbourne, Victoria, Australia
8 Monash University, Melbourne, Victoria, Australia
9 Royal Marsden Hospital, London, UK

Abstract

Introduction: To examine the long-term outcomes of high dose rate brachytherapy boost (HDR-BT) combined with external beam radiotherapy (EBRT) for intermediate and high-risk prostate cancer patients.

Methods: Data from 95 patients who underwent combined EBRT (50.4 Gy) and HDR-BT to the prostate between 2010 and 2017 were retrospectively analyzed. Biochemical progression free survival (bPFS), local recurrence free survival (LRFS), metastatic free survival (MFS) and overall survival (OS) were estimated using Kaplan-Meier method. Regression analysis was conducted to identify important predictors of outcomes.

Results: A total of 24 patients received an initial HDR-BT dose of 18 Gy in three fractions, with the remaining 71 patients receiving 16 Gy in two fractions as per departmental protocol changes. Most patients (88%) received androgen deprivation therapy. A transurethral resection of the prostate (TURP) was performed in 14 patients and hydrogel spacers (HS) were used in 30 patients. Median follow-up was 58 months. The 5-year bPFS, LRFS, MFS and OS were 93%, 100%, 92% and 86%. Univariate regression revealed no statistical association between patient characteristics and time to relapse (all P > 0.1). Lte + grade 2 genitourinary (GU) toxicity was 6.3%. The use of HS or prior TURP had no impact on late GU toxicity. Late Grade 1 gastrointestinal (GI) toxicity was 5.3%.

Conclusion: The combined HDR-BT with EBRT resulted in excellent 5-year bPFS. The cumulative risk of late GU and GI toxicity was low and can be further refined with preventative strategies such as a pre-emptive TURP and/or HS insertion.

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

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

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

Methods

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

Planning and treatment procedure
All men were prospectively followed from initial review. A mini TURP was performed preoperatively in patients with bladder outlet obstruction, confirmed by cystoscopy. The HDR was scheduled at least 3 months post mini TURP. The ADT was recommended for 6 months in patients with intermediate risk and for 24 months in high-risk disease. In patients who agreed to ADT, this was started at least 3 months before the commencement of radiotherapy.

Our HDR-BT using Iridium 192 was performed 2 weeks prior to EBRT. Patients were placed in the semi-lithotomy position under spinal anaesthesia. Three gold fiducial markers were inserted into the prostate to facilitate image guided radiation therapy (IGRT) for both HDR-BT and EBRT. An average of 15 HDR catheters (OncoSmart ProGuide needles, Elekta Pty Ltd, Stockholm, Sweden) were inserted into the prostate transperineally using a template technique (5F prostate stepper template, Elekta Pty Ltd) under transrectal ultrasound guidance. For patients treated from December 2013 (n = 30), polyethylene-glycol HS gel (SpaceOAR™, Augmenix, Waltham, MA, USA) was injected to displace the anterior rectal wall posteriorly from the prostate once all needles were inserted. Under flexible cystoscopy guidance to ensure the vesico-ureteric junction was not compromised, all needles were advanced 2.0 cm into the bladder to account for caudal displacement resulting from perineal oedema.

A computed tomography (CT) scan was acquired for planning and imported into Oncentra® (Elekta Pty Ltd) treatment planning system. The brachytherapy clinical target volume (CTV) was the prostate alone with a 2–3 mm margin to account for microscopic extension, except posteriorly where no margin was applied. The planning target volume (PTV) was the CTV. Dose goals were PTV V100—95%, V150—35%, V200—15%. The rectum was contoured as a whole solid structure beginning at 1.0 cm above the most superior level of the PTV to the anorectal junction. The urethra was contoured using the outer surface of the Foley catheter. Rectal and urethral dose constraints were rectal V75 < 1 cc and urethral V125 < 1 cc. A total of 24 patients received an initial dose of 18 Gy in three fractions from 2010–2011, with the remaining 71 patients receiving 16 Gy in two fractions from 2012 onwards as per our departmental protocol.

Treatment was delivered using a single implant by a remote afterloading 1r192 source (Flexitron, Elekta Pty Ltd) with a minimum of 6 hours between fractions. Our treatment verification technique involved a digitally reconstructed radiograph (DRR) generated from the CT data set as the reference image for HDR catheter position relative to the fiducial markers. Prior to treatment delivery, a 2D image of the pelvis was acquired using a C-arm to assess HDR catheter position. A standard 2 mm action threshold was applied.

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

**Evaluation of response: clinical endpoints**

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

**Statistical analysis**

Descriptive statistics are presented as median and interquartile range (IQR:) for continuous variables and as frequency (percentage) for binary variables. The bPFS, LRFS, MFS and OS rates were estimated using the Kaplan-Meier method. Estimates at specific time points with respective 95% confidence interval (95% CI) were also provided. The association between patient characteristics and disease-specific risk factors and bPFS, MFS and OS was determined using linear regression. Effect estimates were reported as mean difference (MD) with 95% CI. In all analyses, a value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed in R (version 3.1.1; R Development Core Team 2009, Vienna, Austria) using standard and validated statistical procedures.

**Results**

A total of 95 patients with National Comprehensive Centre Network Prostate Cancer Guideline v.3.0 criteria-defined intermediate or high-risk prostate cancer were treated using initial HDR-BT followed by EBRT to the prostate and seminal vesicles between 2010 and 2017. All patients were free of distant metastases at the time of HDR-BT. All patients were classified into low, intermediate or high (very high) risk based on the NCCN 2016 guidelines. A smaller subset also revealed 28 patients to be at very high risk. With a median age of 72.7 years (IQR: 52.83 years) and a median PSA level of 12.4 ng/mL (IQR: 3.2-47.0 ng/mL), the primary tumour staging was reported as T1 (19%), T2 (49%) and T3 (32%) using the Union for International Cancer Control TNM Classification 8th Edition. Most patients (88%, $n=84$) were on ADT prior to therapy, whilst 15% ($n=14$) of patients had undergone prior TURP. All 30 patients underwent successful HS insertion with no postoperative complications reported. Table 1 shows patient demographics and disease-specific characteristics.

**Dosimetric values**

The median prostate V100, V150 and V200 were 95.4% (IQR: 84.3–99%), 32.4% (IQR: 24.9–41.1%) and 12.1% (IQR: 9.6–15.7%). The median rectal V75 was 0.32 cc (IQR: 0.0-1.46 cc) and median urethral V125 was 0.04 cc (IQR: 0.0-1.1 cc). The use of HS was associated with a significantly reduced median rectal V75 of 0.0 cc (IQR: 0-0.22) vs. 0.45 cc (IQR: 0.0-1.46) ($P < 0.001$).

**Disease control**

The median follow up was 58 months (IQR: 7-125 months), with only one patient lost to follow-up because of a move to another country. The 5-year bPFS, LRFS and MFS rate were 92% (95% CI 85-98%), 100% and 92% (95% CI 88-99%), respectively. At 5-years, the overall OS was 88% (95% CI 81-95%). Univariate regression revealed no statistical association between patient

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>$N=95$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T stage</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18 (19.9)</td>
</tr>
<tr>
<td>2</td>
<td>47 (49.4)</td>
</tr>
<tr>
<td>3</td>
<td>30 (31.5)</td>
</tr>
<tr>
<td>ISUP grade</td>
<td></td>
</tr>
<tr>
<td>ISUP grade 1</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td>ISUP grade 2</td>
<td>22 (23.1)</td>
</tr>
<tr>
<td>ISUP grade 3</td>
<td>30 (31.5)</td>
</tr>
<tr>
<td>ISUP grade 4</td>
<td>15 (15.7)</td>
</tr>
<tr>
<td>ISUP grade 5</td>
<td>23 (24.2)</td>
</tr>
<tr>
<td>NCCN risk groups</td>
<td>42 (44.2)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>53 (55.8)</td>
</tr>
<tr>
<td>High risk</td>
<td>53 (55.8)</td>
</tr>
<tr>
<td>ADT</td>
<td>84 (88.4)</td>
</tr>
<tr>
<td>No</td>
<td>11 (11.6)</td>
</tr>
<tr>
<td>Prior TURP</td>
<td>14 (14.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>81 (85.2)</td>
</tr>
<tr>
<td>No</td>
<td>30 (31.6)</td>
</tr>
<tr>
<td>Hydrogel spacer</td>
<td>45 (48.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>24 (25.2)</td>
</tr>
<tr>
<td>No</td>
<td>71 (74.8)</td>
</tr>
</tbody>
</table>

ADT, androgen deprivation therapy; ISUP, International Society of Urological Pathology; NCCN, National Comprehensive Cancer Network; TURP, transurethral resection of the prostate.
risk factors and time to relapse (all P > 0.1) (Table 2). Six patients experienced biochemical relapse at 35 months (IQR: 24–50 months), with the site of recurrence including either bone (n = 3) or regional lymph node (n = 3) metastases. All six patients underwent various treatment options (e.g. node dissection, stereotactic radiotherapy).

Toxicity

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

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

Discussion

The aim of this retrospective case series was to evaluate the safety and effectiveness of HDR-BT combined with

| Table 2. Univariate analysis of risk factors and its impact on bPFS, MFS and OS |

<table>
<thead>
<tr>
<th>Factors</th>
<th>Biochemical progression free survival (bPFS)</th>
<th>Metastasis free survival (MFS)</th>
<th>Overall Survival (OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 yr KM</td>
<td>HR (CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>90%</td>
<td>0.8 (0.2–4.2)</td>
<td>0.81</td>
</tr>
<tr>
<td>≤70</td>
<td>93%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor (T) stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1–2</td>
<td>92%</td>
<td>1.4 (0.2–4.2)</td>
<td>0.75</td>
</tr>
<tr>
<td>T3</td>
<td>91%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISUP (Grade)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 + 2 + 3</td>
<td>91%</td>
<td>0.8 (0.2–4.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>4 + 5</td>
<td>93%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCCN risk</td>
<td>Intermediate High</td>
<td>1.2 (0.1–11.1)</td>
<td>0.89</td>
</tr>
<tr>
<td>Percentage Core +</td>
<td>&lt;50%</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>97%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDR dose</td>
<td>18 Gy/3F</td>
<td>93%</td>
<td>1.4 (0.3–7.0)</td>
</tr>
<tr>
<td>16 Gy/2F</td>
<td>89%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADT</td>
<td>No</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADT, androgen deprivation therapy; F, fraction; Gy, gray; HDR, high dose rate; HR, hazard ratio; ISUP, International Society of Urological Pathology; KM, Kaplan Meier; NCCN, National Comprehensive Cancer Network.

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

Gl, gastrointestinal; GU, genitourinary; HS, hydrogel spacer.

EBRT as measured by biochemical and clinical disease control rates in 95 prostate cancer patients presenting with intermediate and high-risk disease. With a median follow-up rate of 58 months, the combined treatment modality resulted in 5-year bPFS and OS rates of 92% and 88%, respectively. In addition, 32% of patients received hydrogel spacer to improve dosimetric outcomes and minimize adverse events.

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

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

In the study by Khor et al., the authors undertook a matched paired analysis and compared EBRT alone (74 Gy in 37 fractions) versus EBRT (46 Gy in 23 fractions) and HDR-BT (19.5 Gy in 3 fractions) with or without ADT in 344 men with intermediate and high-risk prostate cancer. The 5 and 10 year freedom from biochemical failure was 70.9% and 32.8%, respectively, in the EBRT and HDR-BT cohort ($P = 0.001$). This statistically significant reduction in risk of biochemical failure was independent of ADT usage in the EBRT and HDR-BT cohort, suggesting that this treatment approach was effective regardless of planned ADT usage. However, we were mindful about making any real direct comparisons given the methodological variations seen across the brachytherapy literature. For example, many single centre studies reported on the use of either prostate versus pelvic EBRT; whereas heterogeneity was observed in the prescribed doses, both in terms of total dose and fraction and dose reporting. In addition, various disease risk stratification methods were employed (e.g., EBRT patients were stratified according to the NCCN system, whereas HDR-BT patients were stratified according to NCCN, risk factors and the American Joint Committee on Cancer (AJCC). Different prescribing patterns of ADT administration were also coupled with the use of different criteria to define biochemical failure.

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

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

Late grade 3 GU toxicities were 5.3%, which fell within the ranges seen in a number of published reviews. Similarly our urethral stricture rate of 4.2% was in keeping with a recent review that reported crude rates from 0.14%. However, our rates were significantly lower than other Australian studies, which we attribute to three strategies. First, the precise placement of a gold fiducial marker at the very apex of the prostate under transrectal ultrasound control significantly improved the accurate delineation of the prostatic apex on CT imaging. Second, we minimized any potential threat to caudal movement of the HDR catheters by imaging prior to each fraction and advancing the position of the HDR source within the catheters relative to the gold fiducial markers. Finally, 14 men (15%) underwent a mini TURP before receiving HDR-BT because of bladder outlet obstruction. This preventative strategy widened the prostatic urethral channel and reduced the risk of subsequent urethral strictures.

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

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

Although a series of reviews\(^ {1,6,16}\) highlighted various safety and efficacy profiles of EBRT and HDR-BT combinations, there was still an overall decline in numbers of HDR-BT procedures performed throughout Australia. In the study by Ong et al.,\(^ {9}\) the authors evaluated the pattern of utilization of HDR brachytherapy using the population-based Prostate Cancer Outcome Registry Victoria and government-based Medicare Benefit Schedule statistics. In 1806 men with prostate cancer who had definitive EBRT, only 124 (7%) had documented HDR-BT utilisation with EBRT. More so, there was a significant decline in numbers of HDR-BT performed throughout Australia from 313 cases in 2010 to 125 cases in 2015. Similarly, Orío et al.\(^ {26}\) found in the United States that radiation oncology centres performing one case per week dropped from 6.7% to 1.5% and 4.5% to 2.7% in academic and non-academic practices, respectively. Explanations put forward for this were seen to be multifactorial, but were attributed to the use of various other EBRT techniques such as IMRT.

**Study limitations**

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

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

**References**


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Overview

This retrospective study of a prospectively collected database of all HDR brachytherapy patients treated at Genesis Cancer Care Victoria (Radiation Oncology Victoria) was interrogated from 2010 to 2017 to assess the long-term oncological control and toxicity of combined EBRT and HDR brachytherapy boost (EBRT-HDR boost). The aim of this study was to report the efficacy of EBRT-HDR boost for patients with intermediate to high risk prostate cancer, including cohorts who have had a prior TURP pre HDR brachytherapy and HS insertion.

Of the 95 patients identified, 44% had intermediate risk disease and 56% had high risk disease. The median follow up for all patients was 58 months. The 5-year biochemical PFS for all patients was 92%. The 5-year biochemical RFS for intermediate and high-risk disease were 92% and 88% (p=0.89), respectively. The 5-year overall survival for all patients was 88%. The 5-year overall survival for intermediate and high-risk disease were 91% and 75% (p=0.40), respectively.

Late Grade 2 and Grade 3 GU toxicity was seen in 6.3% and 5.3% of patients, respectively. Patients who had a prior TURP were not at risk of increased acute or late GU toxicity. Acute Grade 1 and Grade 2 GI toxicity was seen in 25.3% and 1.1% of patients, respectively. Late Grade 1 GI toxicity was seen in 5.3% of patients. No late Grade 2 or greater GI toxicity was seen. The risk of acute Grade 1 GI toxicity was significantly less in the HS group compared to the non-HS group (13.3% vs 30.8%, p=0.05).

We have demonstrated excellent 5-year biochemical control for both intermediate and high-risk disease, comparable to that seen in other prospective and retrospective HDR studies. In addition, it is also comparable to that seen for the ASCENDE-RT trial where LDR brachytherapy was used. The risk of late Grade 3 GU toxicity was 5.3%, comparable to our LDR retrospective series and more contemporary HDR reports. We have credited this to the use of IGRT (implantation of gold fiducial markers and assessment of caudal displacement of HDR catheters with perineal oedema), as well as a preventative strategy to widen the prostatic urethral channel with a pre-emptive TURP in order to reduce the risk of subsequent urethral strictures. The risk of significant late GI toxicity was low but the use of HS significantly reduced the risk of acute GI toxicity.

In summary, we have confirmed the efficacy of EBRT-HDR boost for intermediate to high risk prostate cancer with excellent long term biochemical PFS, low risk of late GI toxicity and an
acceptable risk of late GU toxicity. The risk of late Grade 3 GU toxicity can be managed with a change in HDR treatment protocols as well as the aggressive management of patients with pre-existing urethral obstructive symptoms. Significantly, the long-term biochemical control rates can be substantially improved with the use of EBRT-HDR boost when compared to even dose escalated IMRT.
The use of tissue fiducial markers in improving the accuracy of post-prostatectomy radiotherapy

Michael Chao, FRANZCR1,2, Huong Ho, BSc, MSc2, Daryl Lim Joon, FRANZCR1, Yee Chan, FRACS1, Sandra Spencer, Dip App Sci Med Rad2, Michael Ng, FRANZCR2, Jason Wasiak, PhD1, Nathan Jaworszchuk, FRACS, PhD1, Kevin McMillian, FRACS3, Shornik Sengupta, FRACS, PhD1, Alwin Tan, MBBS, FRACS3, George Koufogiannis, FRACS3, Margaret Cokeley, BSc2, Farshad Foroudi, FRANZCR, Doc Med Sci1, Tristan-Scott Khong, BSc3, Damien Bolton, FRACS, PhD1

1The Austin Hospital, Heidelberg; 2Genesis Cancer Care Victoria, Melbourne; 3Box Hill Hospital, Box Hill, The Bays Hospital, Mornington, The Ringwood Private Hospital, Ringwood East, Australia

Purpose: The aim of this retrospective study was to investigate the use of a radiopaque tissue fiducial marker (TFM) in the treatment of prostate cancer patients who undergo post-prostatectomy radiotherapy (PPRT). TFM safety, its role and benefit in quantifying the set-up uncertainties in patients undergoing PPRT image-guided radiotherapy were assessed.

Materials and Methods: A total of 45 consecutive PPRT patients underwent transperineal implantation of TFM at the level of vesicourethral anastomosis in the retrovesical tissue prior to intensity-modulated radiotherapy. Prostate bed motion was calculated by measuring the position of the TFM relative to the pelvic bony anatomy on daily cone-beam computed tomography. The stability and visibility of the TFM were assessed in the initial 10 patients.

Results: No postoperative complications were recorded. A total of 3,500 images were analysed. The calculated prostate bed motion for bony landmark matching relative to TFM were 2.25 mm in the left-right, 5.89 mm in the superior-inferior, and 6.59 mm in the anterior-posterior directions. A significant 36% reduction in the mean volume of rectum receiving 70 Gy (rV70) was achieved for a uniform planning target volume (PTV) margin of 7 mm compared with the Australian and New Zealand Faculty of Radiation Oncology Genito-Urinary Group recommended PTV margin of 10 mm.

Conclusion: The use of TFM was safe and can potentially eliminate set-up errors associated with bony landmark matching, thereby allowing for tighter PTV margins and a consequent favourable reduction in dose delivered to the bladder and rectum, with potential improvements in toxicities.

Keywords: Fiducial marker, Image-guided radiotherapy, Intensity-modulated radiotherapy, Prostatectomy, Prostate cancer

Introduction

Although consensus guidelines are available to help define the clinical target volume (CTV), one of the technical challenges that remain is defining the optimal planning target volume (PTV) expansion. The current post-prostatectomy consensus...
guidelines of the Australian and New Zealand Faculty of Radiation Oncology Genito-Urinary Group (FROGG) recommend a uniform 10-mm margin in all directions to account for daily treatment set uncertainties [1]. As rectal dose constraints can be difficult to achieve, a caveat of a 5-mm posterior expansion is deemed acceptable in these situations. However, this has the potential of increasing the risk of geographic misses.

The use of fiducial markers such as gold seeds and surgical clips placed in the prostate bed has been reported in the literature [2-7]. Although surgical clips have the advantage of being non-invasive, some studies have found them difficult to match because of the varying number and asymmetric shape [5,7]. The use of gold seeds has been found to be reliable as they are easily identifiable, stable and representative of the prostate bed [5-7]. Over the past few years, a radiopaque hydrogel tissue fiducial marker (TFM) called TraceIT (Augmenix Inc., Waltham, MA, USA), has gained considerable interest as a soft tissue marker in assisting with target delineation and treatment verification [8,9]. TraceIT is a particulated injection that is visible on magnetic resonance imaging (MRI), computer tomography (CT), and cone beam computer tomography (CBCT). In addition, it has no CT artefact and creates no dose perturbation.

In this study, the primary endpoint was to investigate the safety, visibility and stability of TFM in its role as a fiducial marker. The secondary endpoints were to determine the required PTV margin expansion using conventional bony landmark versus TFM image-guided radiotherapy (IGRT) and to determine the dosimetric impact of a tighter PTV expansion on rectum and bladder organs at risk (OAR) when TFM IGRT is used.

**Materials and Methods**

1. Study design
A retrospective review of 45 patients who underwent TFM implantation prior to a course of salvage post-prostatectomy radiation therapy (PPRT) was performed. Institutional Review Board approval was obtained prior to commencement of this study. All participants provided written medical informed consent prior to undergoing any therapeutic procedure.

2. Participants
Forty-five consecutive patients referred to one radiation oncologist who commenced PPRT at Genesis Cancer Care Victoria, Melbourne, Australia between January 2016 and November 2017 were included in this study. Eligible patients were consecutive men >18 years of age with histologically confirmed prostate cancer post radical prostatectomy (RP) requiring salvage PPRT. These patients had either a persistent or rising prostate specific antigen (PSA) post RP with or without positive surgical margins, extraprostatic extension or seminal vesicle invasion. The exclusion criteria included known allergy to iodine or contrast, known metabolic disorder, distant metastatic disease, unilateral or bilateral total hip replacement and previous pelvic RT.

3. TFM (TraceIT) injection
Implantation of TFM was performed by one radiation oncologist specialised in prostate brachytherapy. Once the patient was anaesthetised, intravenous prophylactic antibiotic was given. The patient was then set up in the dorsal lithotomy position. Once the patient's perineum, supra-pubic and lower anterior abdomen area were prepped with betadine, a 16F indwelling catheter (IDC) was inserted into the bladder. The IDC balloon was filled with 10 mL of normal saline. Utilising the same brachytherapy principle and equipment, a transrectal ultrasound (TRUS) probe was inserted into the rectum to visualise the bladder, urethra and prostate bed. Gentle traction on the IDC balloon seated at the bladder neck would echographically define the anatomy of the vesicourethral anastomosis (VUA). An 18-gauge disposable brachytherapy grid was attached onto the top of the brachytherapy stepper to help guide the injection of TFM. Using a 18-gauge spinal needle, an average of 0.5 mL of TFM was then injected transperineally on either side of the VUA into the retrovesical tissue (Fig. 1A, 1B). The time taken to perform this procedure was on average 15 minutes. A total of two TFM blebs were injected into each patient. Patients were assessed immediately post-operatively and approximately 5–7 days later to determine the incidence and nature of adverse effects related to the TFM implant.

4. Treatment planning procedure
A pelvic planning CT scan for intensity-modulated radiotherapy or volumetric modulated arc therapy was performed approximately 5–7 days post-TFM implantation. All patients were scanned in the supine position with strict instructions for both bladder and bowel preparation to follow prior to CT simulation and daily treatments. The patients were instructed to empty their bladder and then drink 500 mL of water 1 hour prior to CT simulation and subsequent treatments. An enema was also used prior to CT simulation and for the first
10 fractions of PPRT. This may be continued if the patient failed to maintain an empty rectum during the course of PPRT. CT simulation was performed using a Philips Brilliance Big Bore CT scanner (Philips Medical Systems, Fitchburg, WI, USA) with 3-mm slice thickness. The data sets were electronically transferred to the MIMS v6.7.5 (MIM Software Inc. Cleveland, OH, USA) CT simulation system.
OH, USA) for contouring prior to transferring to Pinnacle v9.8 (Philips Medical Systems) treatment planning system for dosimetry.

The prostate bed or CTV was contoured according to the FROGG guidelines [1]. The normal tissues contoured included the bladder, rectum, VUA, both femoral heads and penile bulb. The implanted TFM were contoured separately and labelled as ‘TFM 1’ and ‘TFM 2’ (Fig. 1C, 1D). A 7-mm uniform expansion was applied to the CTV to create the PTV according to our departmental protocol. All patients were treated daily, 5 days per week on a Varian True Beam linear accelerator equipped with kilovoltage (kV) CBCT capabilities. A prescription dose of 70.2 Gy in 39 fractions was delivered to the PTV, covered by at least 95% of the prescription dose. Rectal dose constraint objectives for the volume of rectum receiving 70 Gy (rV$_{70}$), 60 Gy (rV$_{60}$), 50 Gy (rV$_{50}$), 40 Gy (rV$_{40}$), and 30 Gy (rV$_{30}$) were 20%, 35%, 50%, 60%, and 70% of the rectal volume, respectively. Bladder dose constraints objectives for the volume of bladder receiving 65 Gy (bV$_{65}$) and 70 Gy (bV$_{70}$) were 50% and 35%. The mean penile bulb dose was kept below 25 Gy if achievable.

5. Matching guidelines

Our department imaging protocol for PPRT patients was daily on-line CBCT matched to the TFM using the soft tissue alignment algorithm. The patient was initially set up to skin tattoos, followed by daily on-line CBCT match to the TFM and off-line matching to bony landmark anatomy. Off-sets relative to skin tattoos were recorded in three directions: LR = left (+)/right (–), SI = superior (+)/inferior (–), and AP = anterior (+)/posterior (–). All shifts were recorded in mm. No couch rotation shifts were performed. Mean and standard deviation (SD) of the shift differences were calculated for all 45 patients over all measured fractions for both bony landmark and TFM IGRT. The bony landmark IGRT represented the set-up error and was calculated from the shift of skin tattoos to bony anatomy localisation. The TFM IGRT represented the total position error and was calculated from the shift of skin tattoos to the TFM. The difference in shifts recorded between bony landmark and TFM IGRT represented the improvement in treatment accuracy or inter-fractional prostate bed motion (PBM) when TFM IGRT was compared to bony landmark IGRT. This was used to derive the overall mean systematic error (OM), SD of systematic error (σ), and SD of random error (ε), as previously described by van Herk [10]. The PTV margins were defined in three separate directions (LR, SI, and AP axes) from the entire patient data using the equation formula of $2.5\sigma + 0.7\epsilon$, which is designed to ensure that 90% of patients in the population

<table>
<thead>
<tr>
<th>Week</th>
<th>CBCT</th>
<th>TFM volume mL</th>
<th>p-value</th>
<th>TFM volume mL</th>
<th>p-value</th>
<th>Inter-TFM distance (mm)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1252 (1214–1304)</td>
<td>0.45 (0.20–0.88)</td>
<td>0.06</td>
<td>0.03 (0.03–0.07)</td>
<td>&lt;0.001</td>
<td>14.0 (11–12–22)</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>1255 (1296–1394)</td>
<td>0.44 (0.19–0.83)</td>
<td>0.002</td>
<td>0.11 (0.15–0.89)</td>
<td>0.007</td>
<td>14.1 (11–12–22)</td>
<td>0.11</td>
</tr>
<tr>
<td>3</td>
<td>1240 (1167–1304)</td>
<td>0.41 (0.17–0.63)</td>
<td>0.07</td>
<td>0.05 (0.03–0.07)</td>
<td>&lt;0.001</td>
<td>14.1 (11–12–22)</td>
<td>0.16</td>
</tr>
<tr>
<td>4</td>
<td>1244 (1161–1394)</td>
<td>0.41 (0.18–0.61)</td>
<td>0.06</td>
<td>0.11 (0.15–0.89)</td>
<td>0.01</td>
<td>14.1 (11–12–22)</td>
<td>0.11</td>
</tr>
<tr>
<td>5</td>
<td>1239 (1160–1304)</td>
<td>0.36 (0.13–0.72)</td>
<td>0.16</td>
<td>0.22 (0.15–0.76)</td>
<td>0.26</td>
<td>14.1 (11–12–22)</td>
<td>0.11</td>
</tr>
<tr>
<td>6</td>
<td>1239 (1160–1304)</td>
<td>0.36 (0.13–0.72)</td>
<td>0.16</td>
<td>0.11 (0.15–0.76)</td>
<td>0.06</td>
<td>14.1 (11–12–22)</td>
<td>0.11</td>
</tr>
<tr>
<td>7</td>
<td>1241 (1147–1394)</td>
<td>0.32 (0.13–0.70)</td>
<td>0.06</td>
<td>0.05 (0.03–0.07)</td>
<td>&lt;0.001</td>
<td>14.1 (11–12–22)</td>
<td>0.11</td>
</tr>
<tr>
<td>8</td>
<td>1236 (1168–1304)</td>
<td>0.32 (0.13–0.70)</td>
<td>0.06</td>
<td>0.11 (0.15–0.76)</td>
<td>0.06</td>
<td>14.1 (11–12–22)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Values are presented as median (range). TFM, tissue fiducial marker; HU, Hounsfield unit; CBCT, cone beam computer tomography.
receive a minimum cumulative CTV dose of at least 95% of the prescribed dose.

6. TFM stability, visibility assessment
The visibility and volume stability of the TFMs were assessed in the first 10 patients. The TFM volume in mL, its Hounsfield (HU) maximum and mean values, as well as the inter-fraction distance between the two TFMs placed in each patient were measured. Weekly CBCT images from week 1 to week 8 were imported back to the Pinnacle v.9.8 treatment planning system (TPS) and each bleb were contoured and measured. The change in TFM volume, its HU maximum and mean values and inter-fraction TFM distance from week 1 to week 8 CBCT were assessed for significance using the paired t-test.

7. Planning margins assessment
To further assess the benefits of TFM and its impact on rectal, bladder and penile bulb dosimetry, the first ten consecutive PPRT patients also had a second treatment plan generated with the FROGG recommended consensus PTV expansion of 10 mm around the CTV.

Results

The median age at commencement of PPRT was 68 years (range, 48 to 76 years). The majority of patients (31) had Gleason 7 adenocarcinoma (69%), 1 had Gleason 8 adenocarcinoma, and 13 others had Gleason 9 adenocarcinoma (29%). The primary T staging were pT2 (24%) and pT3 (76%). All patients had detectable PSA levels prior to PPRT, with a level of <0.2 for 62% and >0.2 for 38%. No patients developed bleeding, infection, allergic reactions, urinary retention, rectal perforation or systemic embolization following TFM implantation.

1. TFM stability, visibility and migration
A total of 80 CT and CBCT images were reviewed for the 10 patients assessed. The TFM volume in mL, its HU maximum and mean values as well as inter-fraction TFM distance is found in Table 1. There was no statistically significant difference found except for change in TFM volume in mL from week 6 to week 8. The mean TFM volume was 0.45 mL at week 1 of PPRT, decreasing to 0.33 mL by week 8 of PPRT. This represented a volume loss of 27% over the 3-month period from TFM injection to completion of PPRT. Although there was a significant reduction from week 6 onwards, the TFM remained highly discernible on soft tissue windows as demonstrated by its HU maximum and mean values. The HU maximum and mean values remained stable.

To assess migration of the TFM implanted into the prostate bed, the variations in the TFM distance between fractions and over the course of the treatment were measured. The inter-fraction variation in TFM distance was very small and ranged between 0 to 0.4 mm (mean). As such the migration of the TFM over the course of PPRT was minimal and not significant.
2. Inter-fractional prostate bed motion and set up errors
A total of 3,500 images were assessed. Although the magnitude of shifts was similar for both bony and TFM in both the LR and SI directions, the largest magnitude of error was recorded in the AP direction (Table 2).

Inter-fraction PBM which represents the difference between bony landmark IGRT and TFM IGRT in terms of OM, \( \Sigma \), and \( \sigma \) of PBM in AP, SI, and LR directions is presented in Table 3. Based on the results above, if the patients were matched according to bony anatomy, margins of 2.25 mm along the LR axis, 5.89 mm along the SI axis, and 6.59 mm along the AP axis would be required to ensure the minimum dose to the CTV is at least 95% of the prescription dose in 90% of patients.

3. Impact of 10 mm vs. 7 mm PTV on organ at risk
Table 4 clearly demonstrates a statistically significant improvement in all rectal, bladder and penile bulb dose constraints when a 7-mm PTV margin is compared with a 10-mm PTV margin. A significant 36% reduction in mean \( rV_{70} \) was achieved. In the 10 patients analysed with a 10-mm PTV margin, rectal dose constraints were not met in 6 patients for \( rV_{70} \), in all 10 patients for \( rV_{60} \), in 8 patients for \( rV_{50} \), in 7 patients for \( rV_{40} \), and in 5 patients for \( rV_{30} \). All rectal dose constraints were met in 9 patients with a 7-mm PTV margin. The bladder dose constraints for \( bV_{65} \) and \( bV_{70} \) were not met in 4 patients with a 10-mm PTV margin but achieved in all 10 patients with a 7-mm PTV margin. In addition, an average of 33% reduction was achieved for the mean penile bulb dose for 7 mm margin instead of 10 mm margin.

Discussion and Conclusion
The use of TraceIT as a TFM in our study was found to be safe and efficacious. No significant adverse events were reported. Prior studies have investigated the role of fiducial markers in PPRT used gold seeds or surgical clips as surrogate fiducial markers. Both have been found to be reliable markers, being easily identifiable, stable and representative of the target volume. Although surgical clips have the advantage of being non-invasive, some studies have found them difficult to match [5,7]. In our study, we used a radiopaque hydrogel TFM called TraceIT. The TFM was implanted into the prostate bed and remained fixed within the postoperative tissues, serving reliably as fiducials to target the CTV over the course of PPRT.

Variability was seen between bony anatomy and TFM matching in all axes, with the largest magnitude of shift in the AP plane and the least in the LR plane. We recorded an overall means (SD) of -0.14 (0.53) mm, 0.06 (1.72) mm, and 0.82 (1.81) mm along the SI axis, and 6.59 mm along the AP axis would be required to ensure the minimum dose to the CTV is at least 95% of the prescription dose in 90% of patients.

Values are presented as mean (range).

PTV, planning target volume; OAR, organ at risk; \( rV_n \), volume of rectum receiving dose n; \( bV_n \), volume of bladder receiving dose n.

<table>
<thead>
<tr>
<th>OAR</th>
<th>10-mm PTV margin (%)</th>
<th>7-mm PTV margin (%)</th>
<th>%Reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( rV_{70} &lt;70% )</td>
<td>77 (51–94)</td>
<td>59 (42–79)</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( rV_{60} &lt;60% )</td>
<td>68 (48–88)</td>
<td>48 (37–68)</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( rV_{50} &lt;50% )</td>
<td>60 (43–81)</td>
<td>40 (31–58)</td>
<td>34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( rV_{40} &lt;35% )</td>
<td>51 (37–71)</td>
<td>31 (23–48)</td>
<td>39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( rV_{30} &lt;20% )</td>
<td>22 (11–43)</td>
<td>13 (5–24)</td>
<td>36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( bV_{65} &lt;50% )</td>
<td>40 (12–60)</td>
<td>32 (9–49)</td>
<td>19.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( bV_{70} &lt;35% )</td>
<td>29 (9–47)</td>
<td>22 (5–33)</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Penile bulb (Gy)</td>
<td>30 (14–46)</td>
<td>22.5 (9–37)</td>
<td>25</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean (range).
bladder volume greater than 50% of planning CT volume, and a treatment CBCT rectal size that was within ±2 cm of the planning rectal CT size. Feedback was given daily to our patients and if they failed to meet our image matching protocol, they were duly removed from the treatment couch to allow for correction of bladder filling and rectal emptying before a later attempt at treatment.

The minimum PTV margin required for PBM in our study was 2.25 mm along the LR, 5.89 mm along the SI, and 6.59 mm along the AP axes. The FROGG recommended PTV expansion of 10 mm was adequate to minimise any potential geographic misses with a minimal IGRT standard of bony landmark matching only. Our calculated PTV with the use of TFM and CBCT was similar to the results from Alander et al. [5] who used a combination of gold seed fiducials and CBCT (1.4 mm LR, 5.9 mm SI, and 5.9 mm AP) and Huang et al. [3] who used a combination of clips and CBCT (3.24 mm LR, 5.49 mm SI, and 8.36 mm AP). This was in contrast with the use of gold seed fiducials or surgical clips with orthogonal kV images instead of CBCT where the PTV margins were slightly larger [4,7].

The use of image guidance with fiducial markers and CBCT in PPRT can support the adoption of tighter PTV margins as the risk of geographic misses is minimised. Compared to a 10-mm uniform PTV margin, we observed significant radiation dose reduction in both bladder and rectal volumes as well as a 33% radiation dose reduction in penile bulb dose for our 7-mm PTV margin plan. This is particularly important for our rectal OAR, as it significantly reduced rectal irradiation in the high dose region from $V_{10}$ to $V_{70}$. This is critical because rectal toxicity is correlated with the volume of rectum receiving a particular threshold dose of radiation, particularly $V_{70}$ [11,12]. Therefore, the use of tighter PTV margins can further reduce rectal radiation doses, thus potentially reducing late gastrointestinal toxicity. In addition, smaller PTV margins may allow for a safer means of dose escalation, which can lead to better biochemical control [13-15].

However, our study does have several limitations. Our TFM were implanted at the level of the VUA in the lower prostate bed. The upper prostate bed can move independently of the lower prostate bed due to the close proximity of the bladder and rectum [2]. A pragmatic decision was made to implant the TFM at the level of the VUA in the lower prostate bed as this is the area at highest risk of recurrence post prostatectomy [16-21]. As such this area needs to be targeted as accurately as possible. The upper prostate bed which can tilt in the AP plane is very difficult to correct for, as most treatment couches do not have the ability to tilt or only possess a limited range to do so. Instead we relied on a strict departmental CBCT protocol to reduce the daily variation in bladder and rectal filling to minimise the tilt. In addition, we had a tight imaging tolerance threshold to take the patient off the treatment couch to make corrections to bladder and rectal filling if the parameters were not met. Secondly, we only implanted two fiducial markers into the prostate bed. However, the use of two fiducial markers is not unique and has been found to be effective [6]. It will not allow us to capture potential rotational errors, however a previous study has shown rotational shifts to be very small, and therefore would not be expected to contribute significantly to target motion [22]. Finally, we did not measure intrafractional PBM. Huang et al. [3] who calculated intrafractional PBM in his study showed potential shifts of 2.8 mm along the LR, 3.9 mm along the SI, and 4.3 mm along the AP axes, respectively. However, our departmental PTV margin of 7 mm despite the use of image guidance with TFM and CBCT is sufficient to deal with any intrafractional PBM. As such, we would hesitate against reducing the PTV margin any further.

In conclusion, to our knowledge, this is the first and largest series assessing and supporting the use of a novel TFM with CBCT image guidance in PPRT. The use of TraceIT as a TFM was found to be safe and effective. It had no CT artefact, was stable and highly visible on CT and CBCT. PBM is independent of pelvic bone anatomy. With a PTV margin of at least 6.59 mm required in the AP direction with bony landmark matching, the use of TFM can improve the set-up accuracy, ensuring CTV coverage and reducing bladder and rectal dose despite tighter PTV margins.

**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**References**

Overview
This retrospective study assessed the impact of IGRT with fiducial markers in 45 postprostatectomy patients who underwent salvage dose escalated IMRT at Genesis Cancer Care Victoria (Radiation Oncology Victoria). The prostate bed is not rigid and prostate bed motion can occur both between (inter) and during (intra) a radiotherapy fraction. As such national guidelines have recommended a safety margin (PTV) that encompasses the prostate bed at risk of recurrence (CTV) by 10mm in all directions to account for this setup uncertainty. Unfortunately, this can only increase the volume of critical normal tissues that are exposed to high dose radiation with consequential increased toxicity. The use of IGRT with fiducial markers has been successfully implemented in the intact prostate setting with smaller margins accepted and reduced toxicity. Its implementation in the PPRT setting has not been widely accepted.

In this retrospective study we evaluated the use of tissue fiducial markers (TraceIT) inserted into the retrovesical space on either side of the VUA for image guidance during PPRT. No postoperative complications were recorded. A total of 3500 images were analysed with the calculated prostate bed motion for IGRT without fiducial markers (matched to bone) relative to IGRT with fiducial markers at 2.25mm in the left-right, 5.89mm in the superior-inferior and 6.59mm in the anterior-posterior directions. As such a minimum safety margin (PTV) of at least 7mm would be necessary to account for prostate bed motion to ensure the PTV is adequately covered when using IGRT without a fiducial marker. A 10mm is thus adequate when we also include machine isocentre, matching and imaging uncertainties. However, when IGRT is used with fiducial markers, this safety margin can be reduced significantly to between 5 and 7mm. In addition, the reduction in this safety margin (PTV) can significantly reduce the volume of normal tissues (bladder and rectum) exposed to high radiation dose without compromising the coverage of the prostate bed volume at risk of recurrence (CTV). This may potentially reduce the long-term GI and GU toxicity of PPRT.

As a consequence of our study, the use of tissue fiducial markers and IGRT has become the standard of care in patients undergoing PPRT at Genesis Cancer Care Victoria. In addition, the safety margin (PTV) has been reduced from 10mm to 7mm. Long term follow up of our initial PPRT cohort will continue to provide updates on late GI and GU toxicity.
The introduction of hydrogel spacer to increase prostate to rectal separation and its effect on rectal dosimetry

The use of hydrogel spacer in men undergoing high-dose prostate cancer radiotherapy: results of a prospective phase 2 clinical trial

Michael Chao1,2,3 · Daryl Lim Joon4 · Vincent Khoo2,4,5,6 · Nathan Lawrentschuk2 · Huong Ho1 · Sandra Spencer4 · Yee Chan3 · Alwin Tan7 · Trung Pham8 · Shomik Sengupta2,9 · Kevin McMillan3,9 · Madalena Liu3 · George Koufogiannis3 · Chee Wee Cham7 · Farshad Foroudi2 · Damien Bolton2,3

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Abstract

Objective The purpose of this study was to determine whether the degree of prostate to rectal separation using a hydrogel spacer (HS) and its effect on decreasing rectal dose can be reproduced in the community setting.

Methods Thirty one patients with cT1-3aN0M0 prostate adenocarcinoma receiving radical radiotherapy to 78 Gy were recruited to the study. The primary endpoint was the proportion of patients achieving at least 25% reduction in volume of rectum receiving 70 Gy (rV70). Other endpoints included degree of prostate to rectum separation, HS insertion-related adverse events and the proportion of patients with grade 1 or worse acute or late gastrointestinal (GI) and genitourinary (GU) toxicity.

Results All patients had successful insertion of their HS with no peri-operative toxicity. The mean prostate–rectal separation achieved was 10.5 mm. Twenty nine (93.5%) patients achieved a reduction in rV70 of at least 25%. Acute grade 1 GI toxicity was reported in 3 patients. All symptoms had resolved by 3 months post RT. Late grade 1 GI toxicity was reported in one patient (3.2%) with bowel frequency occurring at 6 months and resolving by 12 months post RT. There was no grade 2 or 3 acute or late GI toxicity seen.

Conclusion In conclusion, this study illustrates that the application and benefits of HS on reducing GI rectal dose endpoints and toxicities during prostate cancer RT can be reliably replicated in a community setting similar to centres participating in the randomised trial under high quality assurance trial monitoring.

Keywords Prostate cancer · Radiotherapy · Hydrogel spacer

Introduction

Randomised control trials and single institution series investigating the use of radiotherapy have demonstrated a dose–response for prostate cancer [1–5]. Whilst advanced radiation therapy (RT) planning techniques such as intensity modulated radiation therapy (IMRT) and volumetric arc therapy (VMAT) have enabled dose escalation to the prostate, it is still limited by potential rectal toxicity due to the close anatomical proximity of the prostate and rectum [6]. It is well documented that late rectal toxicity is correlated to the volume of the anterior rectal wall that receives the highest radiation dose, with 70 Gy especially well established [7, 8].

It is anticipated that reducing dose to the rectum will minimise rectal toxicity. A simple and effective way would be to increase the distance between the rectum and the prostate. This can be achieved by a peri-rectal spacer [9]. One
such example is a synthetic polyethylene-glycol (PEG) based hydrogel spacer (HS). It is injected as a thin liquid into the anterior perirectal fat where it polymerises in situ to form a soft hydrogel after the 2 precursor solutions mix. It maintains organ separation for 3 months and then dissolves and is absorbed by the body within 6 months [10]. Mariados et al. [9] in their randomised trial have reported that the use of PEG HS can substantially reduce the volume of rectum that received 70 Gy by 73.3% with subsequent significant clinical improvement in rectal toxicity.

The aim of this study is to determine whether the degree of prostate rectal separation with PEG HS and its effect on decreasing rectal dose as reported in the Mariados et al. [10] study can be reproduced in a community setting in Melbourne, Australia.

Methods

Following institutional human research and ethics approval, 31 patients were recruited into the study between January 2016 and January 2017. The median follow-up is 12 months (range 6–18 months). All participants provided written informed consent before undergoing any therapeutic procedures.

Study design

Men with clinically staged T1-3aN0M0 histologically confirmed prostate adenocarcinoma receiving radical prostate IMRT to 78 Gy with or without androgen deprivation therapy (ADT) were recruited into the study. Patients who had clinically stage T4 prostate cancer or contraindications to RT (prior RT, connective tissue disease) or MRI were excluded. Patients with intermediate risk disease had ADT for 6 months while those with high-risk disease had ADT for 2 years. RT was commenced 3 months after initiation of ADT. The HS was inserted 2 weeks prior to commencement of RT. A computed tomography (CT) scan was obtained for baseline treatment planning immediately prior to HS insertion. Under general anaesthesia, three gold seed fiducial markers were first inserted into the prostate using a transperineal technique with transrectal ultrasound (TRUS) guidance. This was followed at the same procedure by insertion of the HS using the same technique into Denonvillier’s fascia after hydrodissection with sterile saline. Antibiotic prophylaxis was given to all 31 patients prior to fiducial and HS insertion. Patients were assessed immediately after the procedure and approximately 5–7 days later to determine the incidence and nature of adverse effects related to the HS insertion. After an interval of 5–7 days, patients underwent a second CT and planning magnetic resonance imaging (MRI) scan for IMRT treatment planning. The MRI scans were fused to the planning CT scans to aid with HS volume delineation (see Fig. 1).

All patients were scanned in the supine position with a full bladder and an empty rectum as per departmental protocol. The treatment plans were created on the Pinnacle v. 9.8 (Philips Radiation Oncology Systems, Fitchburg, WI) treatment planning system (TPS). Clinical target volumes (CTV) comprised of prostate and seminal vesicle and were defined in concordance with the Faculty of Radiation Oncology Genito-Urinary Group (FROGG) consensus guidelines [11]. The prescription dose was 78 Gy at 2 Gy

![Fig. 1 T2-weighted magnetic resonance images (MRI) of a patient at baseline/pre-HS (a) and post-HS insertion (b). The HS is 90% water, therefore, has a hyperintense T2-weighted MRI signal](image-url)
per fraction over 39 days, delivered to ≥ 95% of the planning target volume (PTV). The CTV to PTV expansion was 7 mm in all directions except posteriorly, where it was 5 mm (see Fig. 2). Rectal dose constraint objectives for the volume of rectum receiving 78 Gy (rV78), 75 Gy (rV75), 70 Gy (rV70), 60 Gy (rV60) and 50 Gy (rV50) were 5%, 15%, 20%, 35% and 50% of the rectal volume, respectively. All patients received IMRT.

The bladder was contoured from apex to base. The rectum was contoured as a whole solid structure beginning at 1.0 cm above the most superior level of the PTV to the anorectal junction. The HS was contoured on the MRI scan. To determine the effect of the HS for each patient, two treatment plans were created from the baseline pre-HS CT and the post-HS CT/MRI scans. The degree of separation achieved between the anterior rectal wall and the posterior edge of prostate was quantified for the pre-HS and post-HS treatment plans. Rectal dose constraint objectives for rV78, rV75, rV70, rV60 and rV50 were also compared. Prostate volumes, rectal volumes and bladder volumes were also assessed to ensure consistency between the pre-HS and post-HS treatment plans.

Daily cone beam CT verification was performed prior to treatment. Patients were assessed weekly during their treatment and at 2 weeks, 3 months and 6 months follow-up visits for gastrointestinal (GI) and genitourinary (GU) toxicities by their treating radiation oncologist. Their toxicity was recorded using the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

**Statistical assessment**

The primary endpoint was the proportion of patients achieving at least 25% reduction in rV70. This was clinically relevant as the rV70 is correlated with late GI toxicity [7, 8] and the 25% reduction represented the improvement in dosimetry when progressing from three-dimensional conformal RT to IMRT [12]. The three secondary endpoints were (1) mean reductions in rV50, rV60, rV75 and rV78, (2) the degree of prostate to rectum separation achieved with HS and (3) HS insertion related adverse events. The tertiary endpoint was the proportion of patients with grade 1 or worse acute (≤ 3 months of completing RT) or late (> 3 months post RT) GI and GU toxicity.

The Wilcoxon’s signed rank test was used to evaluate the level of significance of observed differences between the pre-HS and post-HS plans. A p value of < 0.05 was considered to be statistically significant.

**Results**

The patient characteristics are detailed in Table 1. Six patients had clinically staged T3a disease, as defined by MRI (six patients). All 31 patients successfully underwent their HS insertion. No patients developed bleeding, infection, allergic reactions, urinary retention, rectal perforation or systemic embolization.

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PSA prostate specific antigen, NCCN National Comprehensive Cancer Network, ADT androgen deprivation therapy

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**Fig. 2** Transverse computer tomographic scan images of prostate delineated in red, hydrogel spacer in yellow and rectum in brown. Gold seed fiducial markers in blue and green. The planning target volume for prostate receiving 78 Gy (PTV78) is delineated in pink and is situated outside the rectum.
The mean and median prostate–rectal distance was 10.5 mm and 10 mm, respectively (range 5–20 mm). The pre-HS and post-HS plans were comparable, with no statistically significant difference between the mean prostate volumes (52.1 cm³ vs 57.4 cm³), mean rectal volumes (73.1 cm³ vs 74.3 cm³) and mean bladder volumes (291 cm³ vs 357 cm³).

All measured rectal dose endpoints recorded a statistically significant improvement with the post-HS treatment plans except for rV78 (Table 2). The mean pre-HS and post-HS rV70 were 13.7% vs 8.0%. Overall, 93.5% of all post-HS plans experienced a >25% reduction in rV70. In addition, 100% of all post-HS plans met all rectal dose constraints compared to only 87% of the pre-HS plans. The bladder dose endpoints were not statistically different.

Acute grade 1 GI toxicity was reported in three patients. All symptoms had resolved by 3 months post RT. Late grade 1 GI toxicity was reported in 14 patients (45%) with bowel frequency and urgency being the predominant toxicity seen. Acute GU toxicity was more frequent, occurring in 30 patients (97%). The majority were grade 1 events, with urinary frequency and urgency being the predominant toxicities. Only 1 patient had a grade 2 acute GU toxicity. Late grade 1 GU toxicity was seen in 14 patients (45%) with the majority being persistent urinary frequency. No urinary incontinence has been observed in our patients.

Discussion

This is one of the largest Australian studies reporting its initial use of HS in prostate cancer radiotherapy. The use of HS in our study was found to be safe and efficacious. No significant adverse events were reported in our study.

The use of HS resulted in a mean prostate–rectal separation distance of 10.5 mm. This is consistent with the separation distance of 12.6 mm reported by Mariados et al. [10] but less than that reported by others (van Gysen et al. [13] or Prada et al. [14]). This may well be related to the learning curve that is inherent in the adoption of any new technique. Pinkawa et al. [15] reported an increase in the mean prostate–rectal separation of 11–15 mm when comparing their first and second cohort of 32 patients. However, even with a smaller mean separation of 10.5 mm we were still able to significantly influence rectal dose endpoints with rV70 reduced by 41%. Uniquely our study cohort differed from the men participating in the randomised trial by Mariados et al. [10] with inclusion of patients with high-risk disease, including six patients with extracapsular extension (ECE). We do not believe there was a risk of posterior displacement of cancer cells by the HS particularly if they had organ confined high-risk disease on MRI or if the ECE was located either anteriorly or laterally. We specifically excluded any patients with clinically staged T4 disease. We did not perform post RT MRI scans as previous studies have reported on its stability in the first 3 months and absorption by 12 months [10].

The use of HS significantly reduced rectal irradiation from rV50 to rV75 relative to the pre-HS plans.

This is important because rectal toxicity is correlated with the volume of rectum receiving a particular threshold dose of radiation. The randomised study by Mariados et al. [10] reported significant relative reductions in rV50, rV60, rV70 and rV80 of 52.3%, 62.9%, 73.3% and 86.3% when comparing pre-HS and post-HS plans. Pinkawa et al. [16] reported a relative reduction of 56% in rV70. Van Gysen et al. [13] also reported a relative reduction of 79.5% in rV70. In our study, we recorded more modest reductions in rV50, rV60, rV70, rV75 and rV80 of 20%, 31.6%, 41.3%, 47.1% and 15.9%. This is the consequence of our departmental policy where the rectal organ at risk (OAR) is delineated as a solid organ from 1 cm above the PTV to the recto-anal junction thereby depicting a shorter length of rectum instead of commencing from the recto-sigmoid junction to the inferior ischial tuberosity. This results in higher rectal dose endpoints. The rV78 for our pre-HS plans were insignificant with a mean of 1.0, therefore, only a small benefit was achieved with the use of HS. Mariados et al. [10] reported a pre-HS rV80 of 4.6%, reducing to 0.6% with HS despite delivering a dose of 79.2 Gy. Importantly, we were able to achieve a mean reduction in rV70 by ≥25%, consistent with the published data [10, 13, 16, 17]. The dose reduction was also reliable, with 93.5% of all post-HS plans achieving a >25% reduction in rV70. In addition, 100% of our post-HS treatment plans met all their rectal dose endpoints, whereas only 87% of the pre-HS treatment plans achieved this goal. The latter will have significant implications for the patient as the prescription prostate cancer dose may need to be lowered to meet the rectal dose constraints with potential implications for cancer control.

With a reduction of RT dose delivered to the rectum, we were anticipating an improvement in toxicity. This has been demonstrated to be significant with only 9.7% of all patients reporting acute grade 1 GI toxicity. Mariados...
et al. [10] reported acute GI toxicity in 32% of their control non-HS patients. Late GI toxicity was observed in only 1 patient (grade 1 bowel frequency at 6 months and resolving at 12 months). No grade 2 or greater late GI toxicity has so far been observed. The reduction in acute GI toxicity is important as patients who experience this are more likely to subsequently develop late GI toxicity [18, 19]. However, longer follow-up is warranted to ensure results are maintained. Haamstra et al. [20] has recently updated the results of the original Mariados study, reporting no change in the 3-year incidence of late grade ≥1 GI toxicity in the HS arm of 2% compared to the non-HS arm of 9.2%. They also reported improved bowel quality of life (QOL) in favour of the HS arm from 6 months onward, becoming significant at 3 years. Of note, Pinkawa et al. [21] has reported sustained improved bowel QOL changes beyond 3 years with their recent 5 year results.

Our acute grade ≥1 GU toxicity of 97% is no different to the HS arm of 90.5% in Mariados et al. [10]. No urinary incontinence has been observed. Haamstra et al. [20] reported a non-significant improvement in urinary QOL for the HS arm. In addition, the rate of grade ≥1 urinary incontinence was significantly lower in the HS arm (15% versus 4%).

We acknowledge a number of study limitations which are not unique to our setting. First, we only have a small sample size. However, this is one of the largest studies reporting the use of HS in Australia. In addition, we were able to demonstrate the reproducibility of the Mariados et al. [10] study for both HS prostate–rectum separation as well as reduction in rV50 to rV75. Second, the follow-up period is short and we may miss late grade 2 GI toxicities given that they are at risk of occurring 17 months (median) after treatment [22]. However, it was reassuring to know that the rate of grade ≥1 GI toxicity did not change with longer follow-up as reported in Haamstra et al. [20]. In addition, we did not record patient-centred outcomes such as health-related or disease-specific quality of life, which have been shown to be significant. Finally, the use of HS in patients with high risk prostate cancer is still open to debate and we will need long-term follow-up to ensure that biochemical control is maintained in these patients.

In conclusion, this study illustrates that the application and benefits of HS on reducing GI rectal dose endpoints and toxicities during prostate cancer RT can be reliably replicated in a community setting similar to centres participating in the randomised trial under high-quality assurance trial monitoring.

Author contributions MC: project development, data analysis, manuscript writing/editing. DLJ: project development, manuscript editing. VK: manuscript editing. NL: manuscript editing. HH: data management, data analysis. SS: data management. YC: data collection. AT: data collection. TP: data collection. SS: data collection. KM: data collection. ML: data collection. GK: data collection. CWC: data collection. FF: manuscript editing. DB: protocol development, manuscript editing.

Compliance with ethical standards

Research involving human participants All procedures performed in this study involving human participants were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

References


Overview
The objective of this prospective phase 2 study was to confirm the results from Song et al. and Mariados et al. Thirty-one patients with localised prostate cancer underwent HS insertion followed by dose escalated IMRT to 78 Gy in 2 Gy fraction sizes. The patients were scanned with CT/MRI prior to HS insertion, followed by repeat CT/MRI after the procedure. IMRT plans were created in both before and after CT/MRI scans, and the dosimetric parameters were compared with one another.

All 31 patients had successful HS insertion with no postoperative complications reported. The use of HS increased the prostate to rectal separation by > 7.5 mm (mean 10.5 mm) in 7% of patients and improved rectal V70 by > 25% in 93.5% of patients. The mean pre-HS and post-HS rectal V70 were 13.7% vs 8.0%. All rectal volume radiation dose endpoints were significantly improved with the use of HS from rectal V50 to V75. In addition, 100% of all post-HS plans met all rectal dose constraints compared to only 87% of the pre-HS plans.

The median follow up was 12 months. Acute Grade 1 GI toxicity was seen in 9.7% of patients. Acute Grade 1 and Grade 2 GU toxicity was seen in 97% and 3% of patients, respectively. Late Grade 1 GI toxicity was seen in 3% (1 patient) and no late Grade 2 or greater toxicity was recorded. Late Grade 1 GU toxicity was seen in 45% of patients. No urinary incontinence has been observed.

In summary, we have reproduced the results of Song et al. and Mariados et al. with significant improvement in prostate to rectal separation and a reduction in rectal V70 of > 25% in the majority of patients. In addition, the incidence of late GI toxicity has been significantly reduced with no Grade 2 GI toxicity recorded, albeit with short follow up. We also reported no urinary incontinence consistent with the randomised study (191). As a consequence of this study, we have now recommended the use of HS in all patients with localised prostate cancer who undergo dose escalated IMRT to improve GI, GU and sexual function.
The use of hydrogel spacer in patients with large prostate volumes and locally advanced disease (cT3a)

Prospective analysis of hydrogel spacer for patients with prostate cancer undergoing radiotherapy

Michael Chao*,†, Huong Ho†, Yee Chan*‡, Alwin Tan§, Trung Pham*, Damien Bolton*, Andrew Troy*, Catherine Temelcos*††, Shomik Sengupta*††, Kevin McMillan†, Chee Wee Cham§, Madalena Liu†, Wei Ding†, Brindha Subramanian†, Jason Wasiak*‡‡, Daryl Lim Joon*†, Sandra Spencer† and Nathan Lawrentschuk*‡‡

*The Austin Hospital, Heidelberg, Vic., Australia, †Genesis Cancer Care Victoria, Ringwood East, Vic., Australia, ‡Ringwood Private Hospital, Ringwood East, Vic., Australia, §The Bays Hospital, Mornington, Vic., Australia, ¶The Valley Private Hospital, Mulgrave, Vic., Australia, **St Vincent’s Hospital, Fitzroy, Vic., Australia, ††Melbourne University, Eastern Health Clinical School, Monash University, Clayton, Vic., Australia, and ‡‡University of Melbourne, Melbourne, Vic., Australia

Objective
To report on the dosimetric benefits and late toxicity outcomes after injection of hydrogel spacer (HS) between the prostate and rectum for patients treated with prostate radiotherapy (RT).

Patients and Methods
In all, 76 patients with a clinical stage of T1–T3a prostate cancer underwent general anaesthesia for fiducial marker insertion plus injection of the HS into the perirectal space before intensity-modulated RT (IMRT) or volumetric-modulated arc RT (VMAT). HS safety, dosimetric benefits, and the immediate- to long-term effects of gastrointestinal (GI) toxicity were assessed.

Results
There were no postoperative complications reported. The mean (range) prostate size was 66.0 (25.0–187.0) mm. Rectal dose volume parameters were observed and the volume of rectum receiving 70 Gy (rV70), 75 Gy (rV75) and 78 Gy (rV78) was 7.8%, 3.6% and 0.4%, respectively. In all, 21% of patients (16/76) developed acute Grade 1 GI toxicities, but all were resolved completely by 3 months after treatment; whilst, 3% of patients (2/76) developed late Grade 1 GI toxicities. No patients had acute or late Grade ≥2 GI toxicities.

Conclusion
Injection of HS resulted in a reduction of irradiated rectal dose volumes along with minimal GI toxicities, irrespective of prostate size.

Keywords
hydrogel spacer, intensity-modulated RT, volumetric-modulated arc RT, #PCSM, #ProstateCancer

Introduction
It is estimated that there will be ~16 665 prostate cancer diagnoses in 2017, resulting in the deaths of >3 452 Australian men [1]. Radiotherapy (RT) remains a highly effective treatment for patients with localised disease. Whilst advanced RT planning techniques, such as intensity-modulated RT (IMRT) and volumetric-modulated arc RT (VMAT), have enabled dose escalation to the prostate and reduced toxicity, it is often associated with increased genitourinary (GU) and gastrointestinal (GI) toxicities, and rectal toxicity in particular. It is well documented that late rectal toxicity is correlated to the volume of the anterior rectal wall receiving a higher dose, especially the volume of rectum receiving 70 Gy (rV70) [2]. Reducing this volume during treatment will minimise rectal toxicity and one of the most simple and effective ways is to increase the distance between the rectum and the prostate.

Although recent advances in RT delivery, including image-guided RT (IGRT), IMRT and VMAT have reduced toxicity rates, it has proven a challenge to spare the anterior rectal wall. Several different methods to reduce the rectal toxicity rate, such as collagen, hyaluronic acid and blood patch, have

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been explored with minimal success [3–6]. Hydrogel spacer (HS) implanted between the prostate and rectum in recent years has gained noticeable interest in increasing the perirectal spacing and reducing RT-related rectal toxicity [7], either in external beam RT alone, low- or high-dose rate brachytherapy, or a combination of both external beam RT and brachytherapy [8,9].

The safety and efficacy of HS in a prostate RT setting have been reported by several studies. More so, two systematic reviews demonstrated minimal acute and early post-RT toxicities [10,11]. However, as with any new technique more information is needed to verify the efficacy of HS, particularly from different regions and centres [12–14]. Therefore, the present study aimed to report on our initial experience of using a HS implant in men with prostate cancer treated with prostate RT.

**Patients and Methods**

**Study Design**

This review of a prospectively collected dataset examined the clinical safety and efficacy of the use of HS between the prostate and rectum (SpaceOAR®; Augmenix Inc., Waltham, MA, USA) for men undergoing a course of IMRT or VMAT. Our institution’s Human Research and Ethics Committee approved our treatment protocol before commencement. All participants provided written medical informed consent before undergoing any therapeutic procedure.

**Participants**

In all, 76 patients with confirmed prostate cancer from Radiation Oncology Victoria, Melbourne, Australia, were enrolled into the study from December 2013 to December 2015. Eligible patients were consecutive men aged ≥18 years with histologically confirmed International Society of Urological Pathology (ISUP) grade 1–5 [15] prostate cancer and with clinically staged T1–T3aN0M0 disease receiving 78 Gy of prostate IMRT. The exclusion criteria included previous pelvic surgery or RT, and a history of Crohn’s disease or inflammatory bowel disease.

**HS Implant Procedure**

Under general anaesthesia and with TRUS guidance, all patients underwent transperineal insertion of three intra-prostatic gold seed markers [7] followed by injection of 8–10 mL HS into the anterior perirectal space between Denonvilliers’ fascia and the anterior rectal wall (Fig. 1).

The HS was implanted by a single radiation oncologist specialised in prostate brachytherapy working in unison with a team of urologists. As there is no simulation available to help with training, important technical expertise of the implantation procedure was disseminated to the urologists by the radiation oncologist, to ensure a high quality insertion of the HS [16].

**Treatment Planning**

Pelvic CT for IMRT/VMAT treatment planning was carried out within 5 days after HS injection. All patients were scanned in the supine position with a full bladder and an empty rectum as per our departmental protocol. The treatment plans were created on the Pinnacle v. 9.8 (Philips Radiation Oncology Systems, Fitchburg, WI, USA) treatment planning system (TPS). Clinical target volumes (CTV) comprised of prostate and seminal vesicle and were defined in concordance with the Radiation Oncology Genito-Urinary Group (FROGG) Consensus Guidelines [17]. The CTV to planning target volume (PTV) expansion was 7 mm in all directions except posteriorly, where it was 5 mm. Rectal dose constraint objectives for the volume of rectum receiving 78 Gy (rV_{78}), 75 Gy (rV_{75}), 70 Gy (rV_{70}), 60 Gy (rV_{60}) and 50 Gy (rV_{50}) were 5%, 15%, 20%, 35%, and 50%, respectively. The radiation dose was 78 Gy in 2 Gy daily over 39 fractions.

The rectum was contoured as a whole solid structure beginning at 1.0 cm above the most superior level of the PTV to the anorectal junction. The HS was identified and quantified by manipulating the window values within the Pinnacle TPS. As our patient cohort did not have planning MRI to aid with visualisation of the HS it was contoured as rectum. The degree of separation achieved between the anterior rectal wall and the posterior edge of the prostate was quantified at the apex, mid-gland, and base. The rV_{78}, rV_{75}, rV_{70}, rV_{60} and rV_{50} were assessed for correlation between dosimetric endpoints and any GI toxicity.

**Data Collection and Follow-up Protocol**

Patients were assessed at baseline, weekly during treatment, and at 3-, 6-, and 12-month follow-up visits and then
annually for any GI symptoms and other adverse events, and for changes in medications or interventions used to treat urinary or rectal symptoms. Toxicity assessment was evaluated and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Acute toxicity was defined as any toxicity occurring during or within 8 weeks of RT. Late effects were considered as events occurring >3 months after treatment or as an event lasting >3 months after treatment.

**Results**

**Patient Demographics**

The 76 patients identified for the study were followed-up over a 2-year period, with only one patient reported lost to follow-up after completing his course of RT. Our population included men with a median (interquartile range [IQR]) age of 74 (60–88) years, presenting with a median (IQR) PSA level of 10.4 (1.1–117) ng/mL. The median (IQR) follow-up was 14 (12–29) months, with the last patient completing treatment in February 2016. Patients’ demographic and disease-specific variables are listed in Table 1.

**Rectal Spacing Outcomes**

Based on the CT planning data, measured perirectal spacing dimensions resulting from HS injection are shown in Table 2. The average achievable spacing was very similar across the entire cohort irrespective of prostate size.

**Dosimetric Outcomes**

Table 3 shows mean achievable rectal dose constraints for our patient cohort with relatively low rectal dose volume in the high-dose region of rV_{70} and rV_{78} (Fig. 2). Most importantly, these improvements were also observed in the larger prostates, as seen in Fig. 3.

**Toxicity Outcomes**

None of the patients reported any rectal bleeding. There were no reports of any adverse events including rectal perforation, or infection after HS injection. In all, 16 patients (21%) developed acute Grade 1 GI toxicity, with all symptoms resolved within 3 months after completion of treatment (Table 4). One patient developed a late Grade 1 rectal haemorrhage at 9 months after treatment; however, this was due to rectal haemorrhoids. One patient developed late Grade 1 proctitis at 8 months after treatment. No patients developed late GI toxicity of Grade ≥2.

Figure 4 is a breakdown of the incidence of acute radiation-induced GI toxicity at various time-points throughout the 8 week course of RT. As expected the incidence was greatest at the conclusion of treatment with all symptoms resolved at 3 months after RT.

In all, 63 patients (83%) developed acute Grade 1 GU toxicity. These symptoms persisted in 18 (24%) patients 3 months after completion of treatment. Two (3%) patients developed a urinary stricture requiring intermittent self-catheterisation (Table 4).

**Discussion**

Progress in RT techniques in recent years has allowed dose escalation with better PTV coverage, significantly improving treatment outcomes with reduced treatment-associated GI toxicities. Our present study demonstrated that HS was well tolerated with no adverse effects associated with the HS, nor any rectal complications reported in our patient cohort.

In lieu of not having a control group and comparing our HS cohort with our current institution’s non-HS patients, the patients receiving the HS implant had rectal dose endpoints that are much lower, particularly in the high-dose region rV_{78}: 0.4% vs 4.5%; rV_{75}: 3.6% vs 9.5%; rV_{70}: 7.8% vs 12.5%; rV_{60}: 14.4% vs 19% and rV_{50}: 27.3% vs 28.5%. This indicates that the application of HS considerably decreased the amount of the anterior rectal volume being treated, with the mean rV_{70} dropping from 12.5% to 7.8% for HS patients. Our present results are in accordance with other published studies [12,14,18,19] and this has further validated our findings. Despite a broad range in prostate size, we also investigated the clinical benefits of HS in larger prostates. Our present study confirmed that rectal dosimetry parameters (Fig. 3) were consistent across the cohort, demonstrating that it is possible to achieve a noticeable reduction in rV_{70} irrespective of prostate size.

### Table 1 Patients’ characteristics.

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We recognise that our rV\textsubscript{70} and rV\textsubscript{75} are marginally higher (Table 5) \cite{3,18} than other studies; however, we attribute this finding to our contouring method. In contrast to some studies \cite{3,14}, where the rectum was contoured from the recto-sigmoid junction to the level of ischial tuberosity, our rectum was contoured from 1.0 cm above the PTV’s upper level to the ano-rectal junction. This resulted in a smaller total rectal volume, which in turn resulted in a higher relative rectal dosimetric parameter.

The relatively large reduction in the high-dose regions was the logical explanation for our decreased patient reported GI toxicities. In particular, only 16 patients (20\%) had acute Grade 1 GI toxicities, which resolved completely (97\%) at 3 months after treatment. The remaining two patients developed either late Grade 1 rectal haemorrhage (one patient) or proctitis (one) at 8 months after treatment. No patients had acute or late Grade \geq 2 GI toxicities. Uhl et al. \cite{20} reported similar low Grade 1 GI toxicities at 12 months and no reported Grade \geq 2 GI toxicities, whilst slightly higher acute and late GI toxicity rates were noted by Uhl et al. \cite{21} and Whalley et al. \cite{12}.

Our present work builds upon published studies examining the use of HS in our region \cite{12–14,22–24}. In particular, our present findings are comparable to three studies \cite{12–14} that have reported on rectal dose endpoints and toxicities (late Grade 1), and found them to be significantly lower across all patient groups, with the greatest difference observed in the higher rectal dose (rV\textsubscript{65–82}) range. More recently, a study by Mariados et al. \cite{18}, examined 222 patients who were randomised to those with HS (n = 149) or without HS (n = 73), whilst undergoing IMRT to a dose of 79.2 Gy in 44 fractions. The authors reported similar results to our present study, with no significant adverse events related to HS injection and no differences in the rates of acute rectal toxicity between the HS and control groups. Another study

### Table 2 Perirectal spacing results.

<table>
<thead>
<tr>
<th>Perirectal spacing, mm</th>
<th>Entire cohort</th>
<th>Prostate size &lt;50 cc</th>
<th>Prostate size &gt;50 cc</th>
<th>Prostate size &gt;100 cc</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>76</td>
<td>29</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>Base</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mm)</td>
<td>10.6 (±2.5)</td>
<td>10 (±2.2)</td>
<td>11 (±2.5)</td>
<td>10.9 (±2.9)</td>
</tr>
<tr>
<td>Median (mm)</td>
<td>11 (5-17)</td>
<td>10 (5-14)</td>
<td>11 (6-17)</td>
<td>11 (7-15)</td>
</tr>
<tr>
<td>Mid-gland</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mm)</td>
<td>7.7 (±2.1)</td>
<td>7.4 (±1.5)</td>
<td>8.1 (±2.3)</td>
<td>8 (±2.2)</td>
</tr>
<tr>
<td>Median (mm)</td>
<td>8 (4-12)</td>
<td>7 (4-11)</td>
<td>8 (2-12)</td>
<td>8 (5-11)</td>
</tr>
<tr>
<td>Apex</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (mm)</td>
<td>4.9 (±1.9)</td>
<td>5 (±1.4)</td>
<td>5.1 (±2.1)</td>
<td>4.5 (±2.1)</td>
</tr>
<tr>
<td>Median (mm)</td>
<td>5 (1-9)</td>
<td>5 (3-8)</td>
<td>5 (3-8)</td>
<td>5 (2-8)</td>
</tr>
</tbody>
</table>

### Table 3 Achievable rectal dose constraint for HS.

<table>
<thead>
<tr>
<th>OAR constraints</th>
<th>HS mean (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rV\textsubscript{50 Gy} \leq 50%</td>
<td>27.3</td>
</tr>
<tr>
<td>rV\textsubscript{60 Gy} \leq 50%</td>
<td>14.4</td>
</tr>
<tr>
<td>rV\textsubscript{70 Gy} \leq 20%</td>
<td>7.8</td>
</tr>
<tr>
<td>rV\textsubscript{75 Gy} \leq 15%</td>
<td>3.6</td>
</tr>
<tr>
<td>rV\textsubscript{78 Gy} \leq 5%</td>
<td>0.4</td>
</tr>
</tbody>
</table>

We recognise that our rV\textsubscript{70} and rV\textsubscript{75} are marginally higher (Table 5) \cite{3,18} than other studies; however, we attribute this finding to our contouring method. In contrast to some studies \cite{3,14}, where the rectum was contoured from the recto-sigmoid junction to the level of ischial tuberosity, our rectum was contoured from 1.0 cm above the PTV’s upper level to the ano-rectal junction. This resulted in a smaller total rectal volume, which in turn resulted in a higher relative rectal dosimetric parameter.

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Our present work builds upon published studies examining the use of HS in our region \cite{12–14,22–24}. In particular, our present findings are comparable to three studies \cite{12–14} that have reported on rectal dose endpoints and toxicities (late Grade 1), and found them to be significantly lower across all patient groups, with the greatest difference observed in the higher rectal dose (rV\textsubscript{65–82}) range. More recently, a study by Mariados et al. \cite{18}, examined 222 patients who were randomised to those with HS (n = 149) or without HS (n = 73), whilst undergoing IMRT to a dose of 79.2 Gy in 44 fractions. The authors reported similar results to our present study, with no significant adverse events related to HS injection and no differences in the rates of acute rectal toxicity between the HS and control groups. Another study
by Pinkawa et al. [25], reported on 167 consecutive patients treated either with HS (n = 110) or without HS (n = 66), whilst undergoing prostate RT up to a maximum dose of 80 Gy. These authors also reported similar findings to our present study, in that the HS injection was found to result in favourable rectal dosimetry with minimal acute rectal toxicity during and shortly after RT.

There are a few key strengths to our present study. Firstly, our present study utilised prospective data collection from a...
large cohort of patients attending a specialist radiation oncology centre in Melbourne, Australia. Secondly, we followed the directives established by the recent consensus statement on the indication and application of HS for prostate RT [26]. Thirdly, we reported minimal acute adverse events during the HS implantation procedure and throughout the 12-month follow-up period. Fourthly, with a single radiation oncologist being involved in the present study, we were quite confident of the level of consistency of the HS injection technique, degree of contouring, and grading of toxicities. Finally, we did not have any restrictions placed on prostate size (i.e. <80 mL) compared to other published data [3,17,19,21], which allowed analysis of the effectiveness of the HS in its ability to increase the perirectal space, irrespective of prostate volume.

The present study has some limitations, which were not unique to our setting and acknowledged in other published studies that also undertook a single institution research activity using cohort or case-series research designs and small sample sizes. Secondly, we may have missed late Grade 2 GI toxicities, given that toxicities are at risk of occurring 17 months (median) after treatment [12]. Thirdly, patients did not undergo pre- and post-imaging with CT, MRI or both to measure prostate rectum spacing and to define the volume of HS inserted. Lastly, we did not record patient-centred outcomes, such as health-related or disease-specific quality of life.

In conclusion, although our present study was limited in its scope, the study provides clinicians with local data about the application and benefits of HS on reducing GI toxicities during prostate cancer RT. However, if further regionally-based research is going to be conducted, studies must consider using multiple radiation oncology centres and stronger study designs that collect patient-focused clinical and non-clinical outcome measures, dosimetric regimens, long-term safety and effectiveness data that includes not only toxicity but also health-related and disease-specific quality-of-life measures.

Conflict of Interest
The authors declare no conflict of interest.

References
7 Ng M, Brown E, Williams A, Chao M, Lawrentschuk N, Chee R. Fiducial markers and spacers in prostate radiotherapy: current applications. BJU Int 2014; 113 (Suppl. 2): 13–20
16 Rashid P, Gianduzio TR. Urology technical and non-technical skill development: the emerging role of simulation. BJU Int 2016; 117 (Suppl. 4): 9–16
20 Uhl M, van Triest B, Ebele MJ, Weber DC, Herfarth K, De Weese TL. Low rectal toxicity after dose escalated IMRT treatment of prostate cancer using an absorbable hydrogel for increasing and maintaining space


**Correspondence:** Huong Ho, Genesis Cancer Care Victoria, 36 Mt Dandenong Road, Ringwood East, Victoria 3135, Australia.

**e-mail:** huong.ho@genesiscare.com.au

**Abbreviations:** (IM)RT, (intensity-modulated) radiation therapy; CTV, clinical target volumes; GI, gastrointestinal; GU, genitourinary; HS, hydrogel spacer; PTV, planning target volume; \( rV(50) (60) (70) (75) (78) \), volume of rectum receiving (50 Gy) (60 Gy) (70 Gy) (75 Gy) (78 Gy); TPS, treatment planning system; VMAT, volumetric-modulated arc RT.
Overview

The analysis of this prospectively collected dataset of 76 consecutive patients with cT1-3a prostate cancer was to evaluate its efficacy in patients with larger prostate volumes and locally advanced disease (cT3a). In addition, we did not perform a planning MRI scan to help delineate the HS volume but instead used our treatment planning system (TPS) to manipulate the CT window values to help identify the HS volume. Of the 76 patients identified, 17% (13 patients) had a prostate volume >100cm³ and 27% (21 patients) had cT3a disease.

All 76 patients had successful HS insertion with no postoperative complications reported. The use of HS was also successful in all 21 patients with cT3a disease. No problems were encountered with their hydrodissection and HS was successfully injected into the perirectal space. The use of HS increased the mean prostate to rectal separation by 7.7 mm in all patients at the mid gland. There was no difference in the mean prostate to rectal separation in patients with prostate volumes of < 50cm³, 50-100cm³ and > 100cm³ with spacing of 7.4 mm, 8.1 mm and 8 mm achieved, respectively. The mean rectal V70 was 7.8% for all patients. There was no difference in the mean rectal V70 for prostate volumes of < 50cm³, 50-100cm³ and > 100cm³ with values of 9%, 8% and 10% achieved, respectively. In addition, we were able to identify the HS volume using our TPS by varying the CT window values to create a differential in the Hounsfield units for the prostate, rectum and HS. This allowed us to identify and delineate the HS volume with accuracy without resorting to a planning MRI. Nevertheless, the use of CT planning alone resulted in marginally smaller mean prostate to rectal separation of 7.7 mm compared to 10.5mm when CT/MRI planning was utilised. However, this did not affect the absolute rectal V70 values (7.8% CT vs 8.0% CT/MRI).

In summary, we were able to successfully implement HS use in patients with large prostate volumes as well as in patients with locally advanced disease (cT3a). However, we do caution its use in patients with cT3 disease and do not recommend its use in patients with cT4 disease. Long term biochemical control data is required before we can implement HS use in patients with cT3 disease. In addition, we were able to use CT planning alone to delineate the HS volume, abrogating the need for MRI planning in every case. However, MRI planning is still the gold standard for HS volume delineation and we would recommend its use for all radiation oncologists who are commencing a HS program. As a consequence of this study, we have recommended the use of HS in patients with large prostate volumes >100cm³.
The use of hydrogel spacer in intermediate and high-risk prostate cancer patients undergoing HDR brachytherapy and EBRT

Improving rectal dosimetry for patients with intermediate and high-risk prostate cancer undergoing combined high-dose-rate brachytherapy and external beam radiotherapy with hydrogel spacer

Michael Chao, FRANZCR,1,2,3 Darren Ow, MBBS,2 Huong Ho, BSc, MSc,2 Yee Chan, FRACS,2,3 Daryll Lim Joon, FRANZCR,2 Sandra Spencer, Dip App Sc Med Rad,1 Nathan Lowentschul, FRACS, PhD,2 Mario Guerrieri, FRANZCR,1 Tiung Pham, FRACS,2 Kevin McMillan, FRACS,2 Alwin Tan, FRACS,2 Farshad Foroudi, FRANZCR,1 Doc Med Sc1, Johann Tang, FRANZCR,1 Jason Wasik, PhD,1 Madalena Liu, FRANZCR,3 George Koufogiannis, FRACS,3 Chee Wee Chiam, FRACS FRCS,4 Damien Bolton, BA FRACS FRCS, MD2,3 Sandra Spencer, Dip App Sci Med Rad1, Nathan Lowentschul, FRACS, PhD,2 Mario Guerrieri, FRANZCR,1 Tiung Pham, FRACS,2 Kevin McMillan, FRACS,2 Alwin Tan, FRACS,2 Farshad Foroudi, FRANZCR,1 Doc Med Sc1, Johann Tang, FRANZCR,1 Jason Wasik, PhD,1 Madalena Liu, FRANZCR,3 George Koufogiannis, FRACS,3 Chee Wee Chiam, FRACS FRCS,4 Damien Bolton, BA FRACS FRCS, MD2,3

1Genesis Cancer Care Victoria, Ringwood East, Australia, 2The Austin Hospital, Heidelberg, Australia, 3Ringwood Private Hospital, Ringwood East, Australia, 4The Bays Hospital, Mornington, Australia, 5National University Hospital, Singapore

Abstract

Purpose: To report on rectal dosimetric and toxicity outcomes of intermediate and high-risk prostate cancer patients undergoing combined high-dose-rate (HDR) brachytherapy and external beam radiotherapy (EBRT) with or without hydrogel spacer (HS) insertion.

Material and methods: A total of 97 patients were analyzed in this study, with 32 patients (33%) who had HS insertion compared with a preceding group of 65 patients (67%) without HS. HS safety, the dosimetric effects on organs at risk (rectal, urethral, penile bulb, and bladder) as well as gastrointestinal (GI) and genitourinary toxicity were evaluated and compared between the two groups.

Results: The median prostate-rectal separation achieved with HS was 10 mm (range, 5-14 mm). There were no post-operative complications following HS insertion. Patients with HS had significantly lower radiation dose to the rectum across all rectal dose volumes from rV30 to rV80, whether in absolute volume (cc) or as percentage of contoured OAR (p<0.001). There was also significantly less acute > grade 1 GI toxicity (12.5% vs. 30.8%, p=0.05) and a trend towards less late grade 1 GI toxicity (0% vs. 7.7%; p=0.11) in the HS group compared to the non-HS group.

Conclusions: Insertion of HS in prostate cancer patients receiving combined HDR and EBRT is safe and has resulted in a significant radiation dose reduction to the rectum, resulting in significantly less acute GI toxicity and a trend towards less late GI toxicity.

Key words: prostate cancer, hydrogel spacer, high-dose-rate, brachytherapy, rectal protection.

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Purpose

The treatment options for men diagnosed with localized prostate cancer have continued to advance over time with relative efficacy seen with various regimes involving radical prostatectomy, external beam radiotherapy (EBRT), and/or brachytherapy [1,2]. Several reviews have also shown that the use of combination therapies such as low-dose-rate (LDR) or high-dose-rate (HDR) brachytherapy and EBRT have allowed for safe radiation dose escalation, which has translated into improved biochemical progression-free survival (bPFS) and metastasis-free survival (MFS) [3,4,5]. However, the benefits of radiation dose escalation with brachytherapy can come at a cost with increased genitourinary (GU) and gastrointestinal (GI) toxicity [6]. Despite advances in treatment delivery and target localization, the rectum remains a primary dose limiting normal tissue due to its close proximity to the prostate.

The use of hydrogel spacers (HS) between the prostate and rectum in recent years has gained considerable interest as it has been shown to safely and effectively increase perirectal spacing between the prostate and rectum, and thus reduce radiotherapy related GI toxicity [7,8,9]. In
this study, we evaluate the use of HS in 32 consecutive patients with intermediate- and high-risk prostate cancer treated with combination HDR brachytherapy and EBRT, and its impact on prostate and normal tissue dosimetry as well as GU and GI toxicity.

Material and methods

This retrospective study examined the clinical safety and efficacy of HS between the prostate and rectum (SpaceOAR®, Augmenix Inc., Waltham, MA, USA) for men undergoing a course of combination HDR brachytherapy and EBRT at the Genesis Care Victoria. Institutional review board approval was obtained to conduct a retrospective review of our prospectively collected dataset of prostate cancer patients undergoing combination HDR brachytherapy and EBRT between 2010 and 2017. Ninety-seven men with intermediate- and high-risk prostate cancer were identified, of whom 32 consecutive patients also underwent HS insertion from 2014 as per our departmental protocol. Dosimetric parameters as well as cumulative acute and late toxicity for the 32 patients who underwent HS insertion were compared with the 65 consecutive preceding patients without HS insertion.

Our initial HDR brachytherapy was performed two weeks prior to EBRT. Patients were placed in the semi-lithotomy position under spinal anesthesia. Three gold fiducial markers were inserted into the prostate to facilitate image-guided radiation therapy (IGRT) for both HDR and EBRT. A total of 14-18 HDR catheters (OncoSmart ProGuide needles, Elekta, Stockholm, SW) were inserted into the prostate transperineally using a template technique (5 f prostate stepper template, Elekta, Stockholm, SW) under transrectal ultrasound guidance with a Flex Focus 400 scanner (BK Medical Aps, Denmark). For patients treated from 2014 (n = 32), HS was injected into the perirectal fat to displace the anterior rectal wall posteriorly away from the prostate once all the HDR catheters were inserted. An 18 G needle was inserted transperineally into the perirectal fat with the tip situated between the mid gland and apex. Hydrodissection with sterile saline was performed to open the potential space between the mid gland and apex. The urethra was contoured using the outer surface of the Foley catheter. The bladder and penile bulb contour was as solid structure in its entirety (see Figure 1). Treatment plans were optimized using an anatomic-based dwell time optimization approach (inverse planning simulated annealing method) with organs at risk (OARs) constraints based on RTOG 0321 (rectal V2<35% < 1 cc, urethral V12<5% < 1 cc, and bladder V3<5% < 1 cc) [11].

A total of 24 patients received an initial dose of 18 Gy in 3 fractions from 2010-2011, with the remaining 73 patients receiving 16 Gy in 2 fractions from 2012 onwards as per our departmental protocol. Treatment was delivered using a single implant by a remote afterloading Ir-192 source (Flexitron Afterloader v. 2.1.3, Elekta, Stockholm, Sweden), with a minimum of 6 hours between fractions. EBRT was commenced within 2 weeks of HDR brachytherapy. A repeat CT simulation scan was performed post-HDR catheter removal with 3 mm slice thickness. The treatment plans were created on the Pinnacle v. 9.8 (Phillips Radiation Oncology Systems, Fitchburg, WI, USA) treatment planning system. The CTV was defined as the prostate and seminal vesicles. The CTV was expanded by 7 mm all around except posteriorly, where it was 5 mm to generate the PTV. All patients were treated with intensity modulated radiotherapy (IMRT) to a dose of 50.4 Gy in 1.8 Gy fractions on a Varian True Beam linear accelerator equipped with kilovoltage (KV) cone beam CT (CBCT). All patients were treated with a full bladder and an empty rectum as per our departmental protocol.

All patients were evaluated at baseline, weekly during the EBRT, and every 3 months for the first year. They were subsequently followed every 6 months until their fifth year and yearly thereafter. Acute toxicity was defined as toxicity occurring during and within the first 90 days after completing their radiation treatment. Late toxicity was defined as toxicity occurring 90 days after their radiation treatment. The GI and GU toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0.

Fig. 1. CT HDR dosimetry with prostate PTV in light red, HS in white, urethra in green and rectum in brown. The 6 Gy and 8 Gy dose lines are outlined in orange and burgundy respectively.
Statistical analysis

Descriptive statistics were used to characterize some of the variables of interest. The Student’s t-test was used to evaluate the level of significance of continuous variables with a normal distribution between the HS and non-HS plans. The Pearson’s chi square test was used to evaluate the significance of categorical variables between the HS and non-HS plans. A p value of ≤ 0.05 was considered to be statistically significant. All analyses were performed using the IBM SPSS Statistics package (v. 24.0).

Results

The median follow-up for the entire cohort was 60 months (12-125 months). The median follow-up for the HS group was 42 months (12-63 months) compared to 65 months (26-125 months) for the non-HS group. The median age was 74 years (52-84 years). The median prostate specific antigen (PSA) was 9.7 ng/ml. Forty-two patients had intermediate-risk disease, while the rest had high-risk disease. Androgen deprivation therapy (ADT) was delivered to the majority of patients (89.7%). The ADT was recommended for six months in patients with intermediate-risk and for 24 months in high-risk disease. In patients who agreed to ADT, the treatment started at least three months before the commencement of radiotherapy. The patient characteristics are shown in Table 1.

HS was successfully implanted into all 32 patients who were planned to receive it. No post-operative complications such as rectal perforation or infection was recorded post HS insertion. The prostate to rectal separation at mid gland was a median of 2 mm (0-5 mm) in the non-HS group versus a median of 10 mm (5-14 mm) in the HS group (p < 0.001).

The median prostate volume and HDR dose delivered to the target volume and OARs are shown in Table 2. There were no significant differences in median prostate volume, prostate V100, and prostate V200 between the two groups. The prostate V150 was significantly improved, with a lower value of 30.5% in the HS group compared with 33.5% in the non-HS group. The use of HS also resulted in significantly lower radiation dose to the rectum and urethra. The median rectal V75 (cc) was 0.45 (0-1.46) in the non-HS group compared to 0.0 (0-0.22) for the HS group. The percentage relative reduction in dose was 100%. All patients with HS met their rectal V75 constraint, whereas only 93.8% (61/65) in the non-HS group accomplished this restriction. The median urethral V125 (cc) was 0.06 (0-1.01) in the non-HS group compared to 0.02 (0-0.66) in the HS group. The percentage relative reduction in dose was 66.7%. All patients with HS met their urethral V125 constraint, while 1 patient in the non-HS group failed to do so. There was no statistical difference in penile bulb radiation dose to 0.1, 1, or 2 cc as percent of prescription dose. In addition, there was also no statistical difference in bladder V70 or V80 between the two groups.

The use of HS with HDR brachytherapy resulted in significantly lower radiation dose to the rectum across all rectal dose volumes from rV30 to rV80, whether in absolute volume (cc) or as percentage of contoured OAR. The impact of HS on rectal dose volumes was most substantial at the highest radiation doses with ≥ 95% relative reduction in rectal V60 to V80, whether in absolute volume (cc) or as percentage of contoured OAR. The impact of HS was still statistically significant at lower radiation doses.

Table 1. Patients’ characteristics of both with and without hydrogel spacer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients</th>
<th>With HS (n = 32)</th>
<th>Without HS (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>74.1 (52.2-84.5)</td>
<td>76.7 (52.2-84.5)</td>
<td>73.4 (60.1-80.8)</td>
</tr>
<tr>
<td>Median PSA (ng/ml)</td>
<td>9.7 (3.2-47)</td>
<td>11.6 (5.6-47)</td>
<td>9.5 (3.2-29.9)</td>
</tr>
<tr>
<td>ADT</td>
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</tr>
<tr>
<td>Yes</td>
<td>87</td>
<td>32</td>
<td>55</td>
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<td>No</td>
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<tr>
<td>T3</td>
<td>31</td>
<td>16</td>
<td>15</td>
</tr>
</tbody>
</table>

HS – hydrogel spacer, PSA – prostate specific antigen, ADT – androgen deprivation therapy
doses, but lower percentage relative reductions were seen in rectal dose volumes from $V_{30}$ to $V_{50}$.

The incidence of acute $\geq 1$ GI toxicity in all patients was 24.7%, with 1.1% developing grade 2 GI toxicity (see Table 4). No acute grade 3 GI toxicities were seen. The incidence of late $\geq 1$ GI toxicity in all patients was 5.2%. No late grade 2 or 3 GI toxicities were observed. There was significantly less acute $\geq 1$ GI toxicity in the HS group compared to the non-HS group (12.5% vs. 30.8%; $p = 0.05$). No patients in the HS group developed acute grade 2 GI toxicity. There was also less late $\geq 1$ GI toxicity in the HS group compared to the non-HS group, but this was not statistically significant (0% vs. 7.7%; $p = 0.11$). The incidence of acute $\geq 1$ GU toxicity in all patients was 91.6%, with 1.1% developing grade 2 GU toxicity. No grade 3 acute toxicity was seen. The incidence of late $\geq 1$, $\geq 2$, and $\geq 3$ GU toxicities in all patients were 44.3%, 6.2%, and 4.1%, respectively. There was no statistical difference in acute or late GU toxicity between the HS group compared to the non-HS group.

<p>| Table 2. Median HDR dose delivered to prostate and organs at risk |</p>
<table>
<thead>
<tr>
<th>Prescribed treatment dose (Gy)</th>
<th>All patients</th>
<th>With HS ($n = 32$)</th>
<th>Without HS ($n = 65$)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median prostate volume (cc)</td>
<td>44.6 (23.3-117.5)</td>
<td>46.7 (30.3-84.5)</td>
<td>43.1 (23.3-117.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>Prostate $V_{100}$</td>
<td>95.4 (84.3-98.9)</td>
<td>94.9 (84.3-97.4)</td>
<td>95.6 (88.1-98.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>$V_{150}$</td>
<td>32.4 (24.9-41.1)</td>
<td>30.5 (24.9-34.8)</td>
<td>33.5 (27.4-41.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>$V_{200}$</td>
<td>12.1 (9.6-15.7)</td>
<td>11.7 (10.4-14.3)</td>
<td>12.2 (9.6-15.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Rectal $V_{75}$ (cc)</td>
<td>0.32 (0-1.46)</td>
<td>0 (0-0.22)</td>
<td>0.45 (0-1.46)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urethral $V_{125}$ (cc)</td>
<td>0.04 (0-1.01)</td>
<td>0.02 (0-0.66)</td>
<td>0.06 (0-1.46)</td>
<td>0.2</td>
</tr>
<tr>
<td>Penile bulb 0.1 cc</td>
<td>0.78 (0.45-1.69)</td>
<td>0.83 (0.45-1.43)</td>
<td>0.76 (0.46-1.69)</td>
<td>0.3</td>
</tr>
<tr>
<td>1 cc</td>
<td>7.84 (4.48-16.95)</td>
<td>8.38 (4.48-14.29)</td>
<td>7.59 (4.64-16.95)</td>
<td>0.3</td>
</tr>
<tr>
<td>2 cc</td>
<td>15.69 (8.97-33.89)</td>
<td>16.65 (8.97-28.58)</td>
<td>15.18 (9.28-33.89)</td>
<td>0.3</td>
</tr>
<tr>
<td>Bladder $V_{70}$ (cc)</td>
<td>4.22 (0.03-13.3)</td>
<td>3.58 (0.3-10.97)</td>
<td>4.37 (0.55-13.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>$V_{80}$ (cc)</td>
<td>2.60 (0.00-9.5)</td>
<td>2.30 (0.00-7.6)</td>
<td>2.86 (0.14-9.5)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Table 3. Median radiation dose to rectum in patients with and without hydrogel spacer

<table>
<thead>
<tr>
<th>Rectal volume (in absolute)</th>
<th>$V_{30}$ (cc)</th>
<th>$V_{40}$ (cc)</th>
<th>$V_{50}$ (cc)</th>
<th>$V_{60}$ (cc)</th>
<th>$V_{70}$ (cc)</th>
<th>$V_{75}$ (cc)</th>
<th>$V_{80}$ (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In absolute volume (cc)</td>
<td>All</td>
<td>14.40 (4.4-40)</td>
<td>7.40 (0.9-21.8)</td>
<td>3.70 (0.7-11.8)</td>
<td>1.70 (0-6.1)</td>
<td>0.65 (0-11.1)</td>
<td>0.32 (0-1.46)</td>
</tr>
<tr>
<td>– Hydrogel spacer</td>
<td>16.50 (6.6-40)</td>
<td>8.60 (3.2-21.8)</td>
<td>4.30 (1.4-11.8)</td>
<td>2.10 (0.3-0.6)</td>
<td>0.86 (0-11.1)</td>
<td>0.45 (0-1.46)</td>
<td>0.20 (0-0.56)</td>
</tr>
<tr>
<td>+ Hydrogel spacer</td>
<td>10.50 (4.4-22.3)</td>
<td>3.60 (0.9-9.9)</td>
<td>1.00 (0.07-4.2)</td>
<td>0.10 (0-1.6)</td>
<td>0.00 (0-0.45)</td>
<td>0.00 (0-0.22)</td>
<td>0.00 (0-0.08)</td>
</tr>
<tr>
<td>% relative reduction</td>
<td>36.4%</td>
<td>58.1%</td>
<td>76.7%</td>
<td>95.2%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>$p$-value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>In percentage (%)</td>
<td>All</td>
<td>18.50 (3.9-44.9)</td>
<td>9.30 (0.8-24.3)</td>
<td>4.50 (0.07-13.1)</td>
<td>2.00 (0-6.5)</td>
<td>0.74 (0-2.5)</td>
<td>0.41 (0-1.4)</td>
</tr>
<tr>
<td>– Hydrogel spacer</td>
<td>20.60 (10.7-44.9)</td>
<td>10.70 (3.2-21.8)</td>
<td>5.50 (2.1-13.3)</td>
<td>2.70 (0-6.5)</td>
<td>1.10 (0-2.5)</td>
<td>0.55 (0-1.4)</td>
<td>0.21 (0-0.66)</td>
</tr>
<tr>
<td>+ Hydrogel spacer</td>
<td>12.20 (3.9-26.4)</td>
<td>4.60 (0.8-17.7)</td>
<td>1.40 (0.07-4.2)</td>
<td>0.10 (0-2)</td>
<td>0.00 (0-0.6)</td>
<td>0.00 (0-0.25)</td>
<td>0.00 (0-0.09)</td>
</tr>
<tr>
<td>% relative reduction</td>
<td>40.8%</td>
<td>57%</td>
<td>74.5%</td>
<td>96.3%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>$p$-value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
The use of HS significantly reduced rectal irradiation from $V_{50}$ to $V_{90}$ compared to the non-HS group. This is important because rectal toxicity is correlated with the volume of rectum receiving a particular threshold dose of radiation. The study by Wu et al. reported significant relative reductions in rectal $V_{50}$ to $V_{90}$ whether in absolute volume (cc) or as percentage of contoured OAR [15]. The median rectal $V_{50}$ (cc) was 0.12 in the non-HS group compared to < 0.005 in the HS group. The percentage relative reduction was almost 100%. This is consistent with our study, where the median rectal $V_{50}$ (cc) was 0.45 (0-1.46) in the non-HS group compared to 0.00 (0-0.22) for the HS group. In addition, the percentage relative reduction in dose was also 100%. Of note, all patients with HS met their rectal $V_{50}$ constraint, whereas only 93.8% (61/65) in the non-HS group accomplished this. For patients who fail to meet their rectal dose constraint, we can either compromise PTV coverage by accepting a lower prostate $V_{100}$ or accept potentially higher rectal toxicity. Yeh et al. also reported lower mean and maximum doses to the rectum with the use of HS [14]. The average mean dose to the rectum was 36% of prescribed dose with no-HS cohort, decreasing to 29% with HS cohort. In addition, the average maximum dose to the rectum was 95% of prescribed dose without HS, decreasing to 78% with HS. Strom et al. reported a significantly reduced rectal D2 cc of 60% without HS compared to 47% with HS [15].

The use of combined brachytherapy (HDR or LDR) with EBRT can lead to increased GI and GU toxicity [11]. When HDR is combined with EBRT, the risk of late grade 3 GI toxicity can be as high as 7%. In the two phase 3 randomized studies comparing HDR with EBRT versus EBRT alone, the risk of late grade 3 GI toxicity was 3.9% in the Sathy et al. study and 7% in the Hoskin et al. study [19,20]. A phase 2 RTOG 0321 study reported a 2.6% combined late grade 3 GI/GU toxicity [11]. A retrospective study by Spratt et al. reported late grade 2 and 3 GI toxicity of 4.1% and 1.4%, respectively for combined brachytherapy and EBRT after a median follow-up of 5.3 years [21]. Yeh et al. delivered aggressive dose escalated HDR brachytherapy of 16 Gy in 2 fractions combined with EBRT of 59.4 Gy in 33 fractions in 326 patients [14]. After a median follow-up of 16 months, the reported rates of acute rectal grade 1 and 2 toxicities were 37.4% and 2.8%, respectively. No acute rectal grade 3 or 4 toxicities were reported. The rates of late rectal grade 1 and 2 toxicities were 12.7% and 1.4%, respectively. In addition, two patients (0.7%) developed late grade 3 rectal toxicity. In our study, the risk of acute ≥ grade 1 GI toxicity was significantly lower in the HS group at 12.5% compared with 30.8% in the non-HS group. The risk of acute grade 2 GI toxicity was minimal in both groups. However, the risk of late grade 1 toxicity...
was 0% in the HS group compared to 7.7% in the non-HS group. Although, this was not found to be statistically significant, the absolute difference between the two groups approaches that seen in the randomized Mariados et al. study of HS in prostate EBRT [7]. Although the risk of both acute and late rectal toxicity is higher in the study by Yeh et al., this is a consequence of their aggressive dose escalation [14]. Despite an EBRT dose of 59.4 Gy following HDR brachytherapy, the reported late rectal grade 3 toxicity of 0.7% can be considered low compared to the two randomized studies. The use of HS may well have contributed to the lower than expected late rectal grade 3 toxicity.

Although we saw a significant difference in urethral $V_{25}$ (cc) between the two groups, the absolute difference was small (0.02 cc in the HS group compared with 0.06 cc in the non-HS group). In addition, the urethral $V_{25}$ was well within the recommended constraint of < 1 cc for the majority of patients. As such, we saw no difference in acute or late GU toxicity between the two groups. It is unlikely that the use of HS would have accounted for the difference in urethral $V_{25}$. Rather, it is likely attributable to the learning curve inherent in the adoption of any new techniques and the improvement in dosimetry seen with the latter cohort of HS patients.

This study also had a number of limitations. A retrospective case series methodology was used, which may introduce a prospective case series methodology was used, which may potential patient selection bias. However, the median prostate volumes and median dose delivered (prostate $V_{150}$) were not significantly different, inferring any improvements seen in OAR dosimetry was the effect of the HS. Secondly, our median follow-up for the HS group was shorter than that for the non-HS group. This may potentially lead to the underestimation of late GI toxicity in the HS group.

Conclusions

The use of HS is safe and effective for patients treated with combined HDR brachytherapy and EBRT. The insertion of HS was successful in all patients who were planned to receive it. This created on average a rectal prostatic separation of 10 mm, which resulted in marked improvements in rectal OAR dosimetry leading to a trend towards fewer acute and late GI toxicity.

Disclosure

Authors report no conflict of interest.

References

**Overview**

This retrospective study assessed the impact of HS insertion in 32 consecutive patients who underwent combined EBRT and HDR brachytherapy boost (EBRT-HDR boost) from 2014 to 2018 on rectal dosimetry and toxicity. They were compared to a preceding cohort of 65 consecutive patients treated without HS from 2010 to 2014.

All 32 patients had successful HS insertion with no postoperative complications reported. The median prostate to rectal separation was increased significantly from 2 mm in the non-HS group compared to 10 mm in the HS group (p<0.001). The use of HS not only significantly lower rectal V75 (cm³) and urethral V125 (cm³) but also significantly improved overall target volume dosimetry (prostate) by reducing the prostate V150. The median rectal V75(cc) was 0.45 cm³ in the non-HS group compared to 0.0 cm³ for the HS group. The percentage relative reduction in dose was 100%. In addition, the use of HS resulted in significantly lower radiation dose to the rectum across all other rectal dose volumes from V30 to V80. The median urethral V125(cm³) was 0.06 cm³ in the non-HS group compared to 0.02 cm³ in the HS group. The percentage relative reduction in dose was 66.7%. There was no difference in prostate V100 meaning the prescribed dose to the prostate was not compromised to achieve better rectal and urethral dose constraints. In fact, the prescribed dose was more homogenous with fewer hot spots within the prostate as demonstrated by the lower prostate V150. As expected, no difference was found in penile bulb or bladder dosimetry.

The median follow up for the entire group was 60 months. However, the median follow up for the HS group is slightly less at 42 months compared to 65 months for the non-HS group. The incidence of acute Grade 1 or greater GI toxicity was significantly less in the HS group compared to the non-HS group (p=0.05). There was also a trend towards less late Grade 1 toxicity in HS group compared to the non-HS group (p=0.11). No difference in acute or late GU toxicity was identified between the two groups.

In summary, we found the use of HS in HDR brachytherapy to be safe and efficacious. We were able to deliver a more homogenous dose to the prostate and improve rectal and urethral dosimetric endpoints. This has translated to a reduction in acute and late Grade 1 GI toxicity. Surprisingly, we had no late Grade 2 or greater GI toxicity. However, we will continue to recommend the use of HS in HDR brachytherapy to ensure we minimise the radiation dose to critical normal tissues such as the rectum and urethra by following the ALARA (As low as reasonably achievable) principle.
14 Post prostatectomy patients with macroscopic prostate bed recurrence undergoing ultra-high dose salvage PPRT

Post Prostatectomy Radiotherapy: Can the urologist help to reduce rectal toxicity?

Abstract

Purpose: To report on feasibility of hydrogel spacer (HS) insertion by for patients undergoing post prostatectomy radiotherapy (PPRT) based on our institutional experience.

Materials and methods: Four consecutive patients referred for PPRT who had biochemical failure in 2 major radiation oncology centers were included. The feasibility of HS insertion was evaluated in each patient. The dose to the rectal wall was estimated in both the post HS and post PPRT setting.

Results: No complications were reported. The mean percentage of rectal volume receiving 70Gy (21.1 pre-HS vs 10.4 post-HS). Only 1 patient developed common terminology criteria for adverse events grade 1 acute gastrointestinal toxicity despite dose escalated PPRT.

Conclusion: We report one of the first series on the feasibility of HS insertion for PPRT, with significant reduction in the high dose rectal volume dosimetry, and hence allows for safer dose escalation to the target volume. The use of HS in the PPRT setting by urologists can help in reducing GI toxicity.

Introduction

Radiotherapy is used in the post-prostatectomy setting, as an adjuvant treatment for patients at high risk of local recurrence,1,2 or as salvage treatment in patients with biochemical failure.3,4 However, some clinicians may argue against indiscriminate use of post prostatectomy radiotherapy (PPRT), especially in the adjuvant setting, given that PPRT is not without morbidity such as rectal toxicities. While late grade 1–2 rectal toxicities are not uncommon, the risk of late grade 3–4 rectal toxicities is often reported to be <5% at PPRT doses of 60–64Gy.5–7 The use of dose escalated PPRT can result in increased late grade 3–4 rectal toxicities.8 Multiple studies have showed that the use of hydrogel spacer (HS), inserted in the anterior peri-rectal space, offers the advantage of anterior rectal wall displacement outside the high-dose radiotherapy region, and thus potentially minimises radiation-related rectal toxicities.8 While we would expect the use of HS for PPRT to result in reduced rectal dosimetry, the feasibility of HS insertion following prostatectomy is unclear, and to our knowledge, there has only been three reports in the literature describing the use of HS in the post-radical prostatectomy (RP) setting.9–11 The aim of our current study is to report on our experience in HS insertion for PPRT, and to compare the rectal dosimetry in the pre-HS and post-HS computer tomography (CT) treatment plans.

Methods

Study population

This is a retrospective series of prostate cancer patients referred for PPRT following biochemical failure in 2 major radiation oncology services in Australia. This study was approved by the Genesis Care Institutional Review Board (IRB). Because of the retrospective design of our study, the IRB waived the need to obtain informed consent from our patients. Patients presenting with biochemical failure had their macroscopic local recurrence proven with either a prostate specific membrane antigen positron emission tomography (PSMA PET) scan and/or on magnetic resonance imaging (MRI) scan. MRI defined recurrences without a positive PSMA PET scan had their local recurrences proven on biopsy of their prostate bed. These patients with macroscopic local recurrences were suitable for dose escalation to the site of gross tumour and were considered for HS insertion.

This is a study on the first 4 consecutive patients who had HS inserted prior to PPRT. The median age was (65–81 years) and all patients underwent a RP between 1-13 years (mean 8 years) prior to presentation. The initial histopathology confirmed Gleason 7–9, pT2c–T3bn0 adenocarcinoma with negative margins achieved in 3 patients. Prostate specific antigen (PSA) at the time of detection in 3 patients, the PSA at presentation ranged from 0.39 to 7, and all had PSA doubling times of ≥6 months. The patient characteristics are detailed in Table 1. All patients had initial staging CT abdomen and pelvis, and whole-body bone scans. A PSMA PET scan was performed in 3 patients and all 4 patients had MRI scans of their pelvis. The MRI scans revealed macroscopic local recurrences in all 4 patients [unifocal recurrence at the right seminal vesicle remnant in 1 patient and vesico-urethral anastomosis (VUA) in 3 patients. The PSMA PET scan confirmed MRI detected local recurrences in 2 patients (Figure 1). The other 2 patients underwent transperineal biopsies of their prostate bed to confirm local recurrence in their VUA. All 4 patients...
had MRI or CT scans that confirmed a clear fat plane between the local recurrence (prostate bed in 3 patients, right seminal vesicle in 1 patient) and the anterior rectal wall.

**Hydrogel insertion**

The non-iodinated HS [ni-HS (SpaceOAR™)] or iodinated HS [i-HS (TraceIT™)] was injected using a transperineal approach between the local recurrence and rectal wall under transrectal ultrasound guidance with the use of a biopsy template after prior hydrodissection with 10 mls of sterile saline. In addition, at least two gold seed fiducials were inserted into the prostate bed on either side of the VUA for image guided radiotherapy (IGRT). The procedure was performed under general anaesthesia and prophylactic antibiotics were administered.

**Radiotherapy planning and treatment**

To determine if there were any adverse effects related to the HS insertion, patients were assessed immediately after the procedure and approximately 5-7 days later. After an interval of 5-7 days, patients underwent their CT scan for intensity modulated radiation therapy (IMRT) treatment planning. MRI scans were performed in 2 patients who had ni-HS inserted and they were fused to the planning CT scans to aid with HS volume delineation.

All patients were scanned in the supine position with a full bladder and an empty rectum as per our departmental protocol. The treatment plans were created on the Pinnacle v9.8 (Philips Radiation Oncology Systems, Fitchburg, WI) treatment planning system (TPS). The low dose Clinical target volumes (CTV) encompassed the prostate and seminal vesicle surgical bed at risk of microscopic disease. The high dose CTV encompassed the macroscopic MRI or PMSA defined local recurrence. The CTV to planning target volume (PTV) expansion was 10 mm in all directions. The prescription dose was 67.2 Gy at 1.6 Gy per fraction to the low dose PTV and 75.6 Gy in 1.8 Gy per fraction to the high dose PTV over 42 days, delivered to >95% of the PTV (D95). Rectal volume radiation dose constraint objectives for rV30 (percentage of rectal volume receiving radiation dose in Gy), rV40, rV50, rV60, rV70, rV75 and rV78 were 80%, 65%, 50%, 35%, 20%, 15% and 5%, respectively.

The bladder was contoured from apex to base. The rectum was contoured as a whole solid structure beginning at 1.0cm above the most superior level of the PTV to the anorectal junction as per departmental protocol. In order to determine the effect of the HS for each patient, two treatment plans were created from the baseline pre-HS CT and the post-HS CT +/-MRI scans (Figure 2). Pre-HS treatment plans were created from either CT simulation scans performed prior to the HS insertion or reconstructed from diagnostic CT scans performed during the patient’s initial workup. The degree of separation achieved between the anterior rectal wall and the posterior edge of prostate bed was quantified for the pre-HS and post-HS treatment plans. The rV30, rV40, rV50, rV60, rV70, rV75 and rV78 were compared. The low dose (67.2Gy) and high dose (75.6Gy) PTV volumes, rectal volume and D95 for PTV67.2 and PTV75.6 were also compared to ensure consistency between the pre-HS and post-HS treatment plans.

**Figure 1** Right seminal vesicle remnant recurrence on (a) computer tomography [CT] and (b) prostate specific membrane antigen positron emission tomography [PSMA PET] scans.

**Figure 2** Pre-hydrogel spacer (HS) and post-HS treatment planning scans showing bladder (solid blue), rectum (solid brown), seminal vesicle recurrence (solid red), low dose PTV (PTV67.2) in green and high dose PTV (PTV75.6) in red. The iodinated HS is hyperintense on computer tomography (delineated by white line) and displaces the rectum posteriorly. The low and high dose PTV transects the rectum in the pre-HS treatment planning scan but is situated on the anterior surface of the rectum post-HS.
Table 1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65</td>
<td>75</td>
<td>66</td>
<td>81</td>
</tr>
<tr>
<td>Year of RP*</td>
<td>2009</td>
<td>2006</td>
<td>2016</td>
<td>2004</td>
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<tr>
<td>Gleason Score</td>
<td>3+4</td>
<td>3+4</td>
<td>4+5</td>
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<td>pTNM</td>
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<td>T2cN0M0</td>
<td>T3bN0M0</td>
<td>T3aN0M0</td>
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<td>Margin Status</td>
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<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Year of presentation</td>
<td>2017</td>
<td>2017</td>
<td>2017</td>
<td>2017</td>
</tr>
<tr>
<td>PSA* at presentation (ng/ml)</td>
<td>7.1</td>
<td>2.3</td>
<td>0.4</td>
<td>0.45</td>
</tr>
<tr>
<td>PSADT^</td>
<td>&gt;1 year</td>
<td>&gt;6 months</td>
<td>&gt;1 year</td>
<td>&gt;1 year</td>
</tr>
<tr>
<td>MRI$</td>
<td>24mm R seminal vesicle recurrence</td>
<td>13mm LVUA</td>
<td>17mm VUA</td>
<td>25mm VUA</td>
</tr>
<tr>
<td>PSMA PET%</td>
<td>R seminal vesicle</td>
<td>LVUA</td>
<td>No uptake seen</td>
<td>Not performed</td>
</tr>
<tr>
<td>Biopsy</td>
<td>Not performed</td>
<td>Not performed</td>
<td>R prostate bed (GS 4+3)</td>
<td>Bilateral prostate bed (GS 4+4)</td>
</tr>
</tbody>
</table>

*RP, radical prostatectomy; *PSA, prostate specific antigen; *PSADT, PSA doubling time; $MRI, magnetic resonance imaging; %PSMA PET, prostate specific membrane antigen positron emission tomography; &GS, gleason score

**Results**

None of the 4 patients reported bleeding or infection following the insertion of HS. There were no allergic reactions or reports of urinary retention, tenesmus or rectal ulceration following the insertion of HS. We were able to evaluate the pre-HS and post-HS plans and found them comparable, with no significant differences between the PTV low and high dose volumes, the rectal volumes and the PTV low dose and high dose volume dosimetry (Table 2). The distance between the rectal wall and local recurrence was increased from immediate vicinity to a mean of 12mm (11-16.5mm) after HS insertion. The HS did not have an impact on rectal volume radiation dose endpoints until at least 60 Gy with a more significant influence at higher doses (Table 3). The difference between pre-HS vs post-HS plans were 20.3% for rV60; 51% for V70; 92.9% for V75 and 100% for V78. The median follow up post IMRT is 16 months (range 14-16 months). Two patients have achieved undetectable PSA levels while the other two have experienced continuing drop in their PSA level to 0.4 ng/ml and 0.2 ng/ml. Only 1 patient developed common terminology criteria for adverse events (CTCAE) grade 1 acute gastrointestinal (GI) toxicity. So far, there has been no late GI toxicity reported.

<table>
<thead>
<tr>
<th>Structure Volumes</th>
<th>Pre-HS* (mean + SD^)</th>
<th>Post-HS* (mean + SD^)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>+PTV67.2 (low-dose) Volumes (cc)</td>
<td>365.8 + 35</td>
<td>355 + 18.1</td>
<td>P=0.35</td>
</tr>
<tr>
<td>+PTV75.6 (high-dose) Volumes (cc)</td>
<td>100.3 + 14.3</td>
<td>99.8 + 13.7</td>
<td>P=0.9</td>
</tr>
<tr>
<td>+PTV67.2 (low-dose dosimetry) D95#</td>
<td>97.8 + 2</td>
<td>98.1 + 0.5</td>
<td>P=0.78</td>
</tr>
<tr>
<td>+PTV75.6 (high-dose dosimetry) D95#</td>
<td>97.1 + 1.3</td>
<td>97.5 + 0.6</td>
<td>P=0.47</td>
</tr>
<tr>
<td>Rectum (cc)</td>
<td>70.5 + 4.8</td>
<td>62.8 + 6.5</td>
<td>P=0.09</td>
</tr>
</tbody>
</table>

*HS, hydrogel spacer; ^SD, standard deviation; +PTV, planning target volume; #D95, prescription dose delivered to 95% of planning target volume
Discussion

We report the feasibility of HS for PPRT, with significant reduction in the rectal dosimetry. The insertion of HS in our series of 4 patients resulted in a median of 12 mm (11-16.5 mm) posterior displacement of rectal wall, and 51% reduction in rV70. Apart from two case reports by Pinkawa et al. and Arcangeli et al., and a series of 32 patients reported by Yeh et al. in abstract, this is only the fourth and second largest series on the use of HS with PPRT. Several studies have shown the oncological benefits of dose escalation in PPRT. In a single institution study in US, Valicenti et al. reported that the 3-year biochemical relapse free survival (bRFS) was better with PPRT dose of >61.2 Gy in the adjuvant setting (90% vs. 64%), and PPRT dose of >64.8 Gy in the salvage setting (52% vs 18%). Given the evidence for higher doses in PPRT, multiple national guidelines, including the American Society for Radiation Oncology/ American Urological Association guidelines, the German Prostate Cancer Guidelines, and the Australian and New Zealand Radiation Oncology Genitourinary Group guidelines, have all recommended RT doses in the range of at least 64-66 Gy for salvage PPRT versus 60 Gy for adjuvant PPRT. However, there is emerging data for even higher doses, with Cozzarini et al. reporting improved 5-year bRFS (83% vs. 71%), and disease free survival (94% vs. 88%), for dose escalated PPRT to >70.2 Gy compared to <70.2 Gy. In a systematic review, King et al. reported that the dose response fits a sigmoidal curve for PPRT and parallels that for definitive radiation therapy (RT) for localised disease, with a dose of 70 Gy achieving 58.6% bRFS vs 38.5% for 60 Gy. The expected proportional gain in bRFS is 2% per incremental Gy. The ongoing phase 3 Swiss Group for Clinical Research 09/10 trial will randomise patients without macroscopic disease to either 64 Gy or 70 Gy and will help provide further insight into the value of dose escalation. In the setting of macroscopic disease, our departmental protocol encourages the use of dose escalated PPRT as recommended by Ost et al. where possible.

However, given the proximity of rectum to the prostatic bed, dose escalation for PPRT can be associated with increased rectal toxicities. Goenka et al. reported their late grade 2/3 genitourinary (GU) and GI toxicities for their IMRT cohort receiving ≥70 Gy at 16.8% and 1.9%. Ost et al. delivered far higher PPRT doses with a median of 76 Gy and reported late grade 2/3 GU and GI toxicities at 22% and 8%. Ohri et al. reported increased late gastrointestinal toxicity in PPRT by 1.2% per Gray. The use of HS to increase the spatial separation of rectal wall from the high dose region is therefore an appealing approach to reduce the rectal dosimetry, while allowing for dose-escalation to the target volume (gross tumor). The use of HS has been well established in the setting of intact prostate RT with the randomised SpaceOAR study by Mariados et al. demonstrating a reduction in rV70 from 12.4% to 3.3%, a relative reduction of 73.3% in favour of the HS patients. This translated to a reduction in late rectal toxicity from 9.2% to 2%, with no late grade 2 or greater toxicity seen at 3 years. In addition, bowel quality of life score (QOL) benefits as measured by the Expanded Prostate Cancer Index Composite tool has consistently favoured the HS patients from 6 months onward, with the difference at 3 years >5 points, meeting the threshold for a minimally important difference. This has also been confirmed by Pinkawa et al. with bowel QOL improvement continuing to 5 years for the HS cohorts.

However, insertion of HS for PPRT can be challenging, given that the plane for HS insertion is less well-defined following prostatectomy. This is in contrast to HS insertion in the intact prostate RT setting, whereby there is a well-demarcated prostatic capsule and the HS is inserted into the potential space immediately posterior to the Denovillier’s fascia. One of the concerns that need to be taken into consideration during insertion of HS for PPRT is the possibility of posterior displacement of cancer cells. This may lead to under-treatment of the cancer cells, posterior to the HS, and may therefore compromise on the oncological control. A prerequisite for HS insertion was successful hydrodissection between the local recurrence and rectal wall, as this would have been impossible in the setting of rectal wall cancer infiltration. Hence, it is important that we carefully select patients in who there is convincing macroscopic local recurrence, and where there is no ambiguity as to whether there is involvement of the anterior rectal wall.

Reassuringly, the anterior rectal wall has not been shown to be common site of local recurrence following RP, which suggest that there is potential role for HS in most patients with macroscopic local recurrence. Earlier studies using transrectal ultrasound guided biopsies to identify the site of biochemical failure following RP showed that the peri-anastomotic site was the most common site of recurrence, with incidence in the range of 60%, MRI studies among patients with local recurrence also showed that large majority of recurrence sites were peri-anastomotic, retro-vesicle, and seminal vesicle.

It is important to acknowledge several limitations of this study. This is a retrospective study, based on the experience of a single urologist and radiation oncologist in a highly-selected group of
patients. We do acknowledge that this is our early experience with HS insertion for PPRT. Pinkawa et al has previously demonstrated a learning curve in the insertion of HS in the intact prostate. In this study, the first cohort of 32 consecutive patients had increased mean distance between prostate and anterior rectal wall (1.5cm vs. 1.1cm), and significantly lower rectal V70Gy (6% vs. 2%) compared with the second cohort of 32 patients. With increase experience, we would also expect to achieve better and more symmetrical HS insertion and better rectal dosimetry in the PPRT setting.

Conclusion
In conclusion, we report the largest series on the feasibility of HS insertion for PPRT, with significant reduction in the high dose rectal volume dosimetry, and hence allows for safer dose escalation to the gross tumor volume (local macroscopic recurrence). The use of HS was found to be effective as a spacing agent in this small series of post RP patients.

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Conflicts of interest
Nil.

References


Overview
This retrospective study assessed the impact of HS insertion in 4 patients who underwent salvage ultra-high dose escalated IMRT for pathological and/or image confirmed macroscopic prostatic bed recurrence postprostatectomy at Genesis Cancer Care Victoria (Radiation Oncology Victoria). A dose response relationship has been identified for PPRT with >66Gy recommended for salvage EBRT. In the setting of macroscopic disease, the recommended dose is >72 Gy and preferably 76 Gy. Due to the unacceptable risk of Grade 3 toxicity, IMRT is preferred over 3DCRT. However, even with IMRT, the risk of late Grade 2 or greater toxicity increases with increasing radiation dose.

In this study, we performed ultra-high dose escalated IMRT to 75.6 Gy in patients with confirmed macroscopic prostatic bed recurrences. ADT was prescribed to all patients. The radiation dose was not compromised despite the use of ADT as we do not know its impact on local control. Two patients had hydrogel spacer (SpaceOAR) while the rest had iodinated hydrogel spacer (TraceIT) inserted. Iodinated hydrogel spacer is visible on CT and obviates the need for a planning MRI. The patients were scanned with CT with or without MRI prior to HS insertion, followed by repeat CT with or without MRI after the procedure. IMRT plans were created in both before/after CT scans and the dosimetric parameters were compared with one another.

All 4 patients underwent successful insertion of their HS with no postoperative complications reported. No problems were encountered with their hydrodissection and HS was successfully injected into the perirectal space. The use of HS increased the mean rectal to local recurrence separation from immediate vicinity to 12 mm. A significant reduction in high dose rectal dosimetry was achieved from rectal V70 to V75. The difference between pre-HS vs post-HS plans were 51% for rectal V70 and 92.9% for rectal V75, respectively. The median follow up was 3 months allowing for assessment of acute GI toxicity. Only one patient developed acute Grade 1 GI toxicity, with no Grade 2 or Grade 3 GI toxicities reported.

The improvement in high dose rectal dosimetry with HS use was not surprising. However, the less than expected reduction in lower dose rectal dosimetry was as the EBRT studies had shown an improvement in all rectal volume radiation dose endpoints. This is likely related to the targeted use of HS in our study, where a smaller quantity of HS was used to displace the rectum from the site of local recurrence. As we were boosting the site of local recurrence, this was the area that required maximal ultra-high dose radiation (75.6 Gy) while the other areas at potential microscopic risk of recurrence was treated to a lower dose (67.2 Gy). The risk of acute GI toxicity was minimal.
and long term follow up is required to fully assess the impact of HS use on late GI toxicity. We did not report acute GU toxicity in our publication but all 4 patients developed grade 1 toxicity. We are in the process of updating our patient cohort with particular interest in oncological control and late toxicity.

In summary, we have demonstrated the feasibility of HS insertion in postprostatectomy patients that require PPRT. This has allowed for significant reduction in high dose rectal volume dosimetry and allows for potentially safer radiation dose escalation. We are excited about the use of HS in postprostatectomy patients without an obvious macroscopic recurrence and will endeavour to perform a prospective phase 2 study to test its feasibility.
15 Conclusion

The aim of this thesis was to investigate strategies that can be employed to improve the oncological outcomes of PC treatment with RT. The use of EBRT has significantly changed with the introduction of IGRT and IMRT allowing unprecedented dose escalation to occur. However, despite increasing the dose to the prostate, there are still limitations with an EBRT alone approach with normal tissue (bladder and rectum) dose tolerances frequently exceeded with consequential increased toxicity. The use of brachytherapy with either an LDR or HDR approach allows for further dose escalation to be realised without further stretching the dose tolerances of normal tissues. In recent years we have seen a decline in the use of brachytherapy for PC either as monotherapy or in combination with EBRT.

The first aim of this thesis was to affirm the safety and effectiveness of brachytherapy in prostate cancer RT by interrogating our prospective brachytherapy database at Genesis Cancer Care Victoria. In Chapter 7, we reported excellent long term bRFS and OS in a large cohort of low risk to intermediate risk PC patients treated with LDR monotherapy. In addition, the risk of long-term significant Grade 3 GI and GU toxicity was low. We also demonstrated the ability to perform LDR monotherapy in patients who have had a prior TURP with equivalent bRFS and OS, and also an acceptably low risk of late Grade 3 GU toxicity. In Chapter 8, we explored the use of LDR brachytherapy in combination with EBRT in patients with predominantly unfavourable intermediate risk PC. In a smaller cohort of 31 patients, we reported excellent long term bRFS and OS with a low risk of late Grade 3 GU toxicity, comparable to our results for patients undergoing LDR monotherapy alone. This is consistent with the outcomes reported by the Seattle Prostate Cancer Group and the NRG Oncology trial. It is significantly lower when compared with the ASCENDE-RT trial. As such we are confident that our contemporary LDR technique can deliver far superior oncological outcomes in patients with higher risk PC when compared to EBRT alone without unduly increasing the risk of late Grade 3 GU toxicity. In Chapter 9, we reported our long-term oncological results in patients undergoing HDR brachytherapy in combination with EBRT in patients with intermediate and high-risk PC. Almost 100 patients were included in the study, with excellent bRFS and OS reported in the entire cohort. The risk of late Grade 3 GI and GU toxicity was also low. In addition, we also demonstrated that a prior TURP was not a contraindication to future HDR, with no increase in late Grade 3 toxicities reported. In summary, we have demonstrated the safety and effectiveness of brachytherapy whether LDR or HDR with
or without EBRT in all prostate cancer risk groups. The use of brachytherapy allows for further prostate cancer dose escalation above and beyond that of EBRT alone.

The contemporary delivery of EBRT in prostate cancer will always include the use of fiducial markers to improve the accuracy and precision of RT (whether IMRT or 3D-CRT). IGRT with fiducial markers have been shown to be significantly superior compared to the use of IGRT with bone matching algorithms. The improvement in CBCT imaging has also permitted the use of IGRT with soft tissue analysis for intact prostates and is preferred in some centres. However, the use of IGRT with fiducial markers and soft tissue analysis for intact prostates is still seen as the most effective approach at my institution. The use of IGRT in PPRT is still contentious, despite the knowledge of interfractional prostate bed motion. Most contemporary radiation oncology centres will utilise IGRT with bone matching algorithms. However, the prostate bed can move independently of pelvic bony anatomy. Even the use of IGRT with CBCT and soft tissue analysis is unable to visualise the inferior extent of the PTV (VUA) accurately. The VUA is the commonest site of recurrence post prostatectomy and needs to be targeted accurately. The use of fiducial markers implanted into the retrovesical tissues at the level of the VUA can potentially improve the accuracy of PPRT. The second aim of this thesis was to investigate the utility of IGRT with fiducial markers in PPRT. In Chapter 10, a radiopaque tissue fiducial marker (TraceIT) was implanted successfully into the retrovesical tissue at the level of the VUA prior to IMRT with no postoperative complications. The calculated prostate bed motion was most significant in the anterior-posterior direction at 7mm, which corroborates the Faculty of Radiation Oncology Genitourinary Group (FROGG) recommended guidelines of a 10mm safety margin to account for motion. However, with the use of fiducial markers, our radiation oncology department has now reduced this safety margin to only 7mm. This practice changing study has allowed more PPRT patients to be treated at the recommended doses with markedly less rectal volume exposure to high radiation doses.

In the last decade, we have seen clinical outcomes in prostate cancer improve with the use of dose escalated image guided EBRT. As a consequence, survivorship is now more important than ever, with quality of life in these patients deservedly gaining more attention. As GI toxicity is nowadays considered to be the main limitation in EBRT for prostate cancer, efforts have been undertaken to achieve improved sparing of the rectum and consequently decrease the risk of GI toxicity. One approach to prevent large rectal volumes from being exposed to high radiation doses is to artificially increase the distance between the prostate and anterior rectal wall using an implantable
rectal spacer. The third aim of this thesis was to implement the use of HS in prostate EBRT with or without brachytherapy. Our goal was to determine its safety, its efficacy in providing adequate prostate to rectal separation, its influence on normal tissue (bladder and rectal) radiation dosimetry and finally, its impact on acute and late GI and GU toxicity. In Chapters 11 and 12, we reported no postoperative complications following the insertion of HS in 107 patients. The use of HS resulted in a mean prostate to rectal separation of 10.5mm when CT/MRI planning was performed. We were also able to delineate HS using CT planning alone by varying the CT window levels to create contrast between the prostate, HS and rectal interface. This was adequate for the purposes of HS demarcation without resorting to another costly MRI scan. When this was performed, we saw a slight reduction in the mean prostate to rectal separation to 7.7mm but this was not clinically significant. The use of HS improved the rectal V70 by >25% in 93.5% of patients. All other rectal volume radiation dose endpoints were also significantly improved with the use of HS from rectal V50 to V75. In addition, we also reported no difference in mean prostate to rectal separation in patients with larger prostate volumes (>100cm³). We were also able to successfully implement the use of HS in patients with cT3a disease. After a median follow up of 12 months, we reported a low incidence of late GI toxicity with no urinary incontinence. The incidence of late Grade 1 GI toxicity was 3%, with no Grade 2 or greater GI toxicities seen. This is consistent with the results of the HS randomised trial. In Chapter 13, we reported the use of HS in prostate cancer patients undergoing HDR brachytherapy combined with EBRT. No postoperative complications were seen and the median prostate to rectal separation was increased to 10mm in the HS cohort of patients. The use of HS not only significantly reduced rectal V75 (cm³) but also urethral V125 (cm³). The incidence of acute Grade 1 or greater GI toxicity was significantly reduced in patients with HS. In Chapter 14, we extended the use of HS to postprostatectomy patients with macroscopic recurrences requiring ultra-high dose PPRT. In the setting of macroscopic disease, the recommended dose for salvage PPRT is >72Gy and preferably 76Gy. However, this ultra-high dose of PPRT can dramatically increase the risk of GI toxicity. We inserted HS into four post-prostatectomy patients with macroscopic disease, successfully achieving a mean rectal to local recurrence separation of 12mm without postoperative complications. A significant reduction in rectal volumes receiving high to very high doses of radiation was seen. The use of HS has not only permitted us to deliver ultra-high dose PPRT that is normally not achievable but also allowed us to do so safely.

Future Directions
The use of LDR or HDR brachytherapy in prostate cancer with or without EBRT is safe and effective. Although its utilisation has diminished in recent years, we have presented excellent bRFS and OS to justify its inclusion as an option in the treatment of prostate cancer belonging to any risk category from low to high-risk disease. This treatment option needs to be at the forefront of all stakeholders from advocacy groups, to patients, to urologists, and equally if not more so, to radiation oncologists themselves. The marked improvement in bRFS seen in patients undergoing combination LDR brachytherapy and EBRT compared to dose escalated contemporary EBRT alone in the ASCENDE-RT study justifies its discussion and recommendation as an option in patients who choose a radiotherapy pathway. This marked improvement in bRFS has been shown to improve long term metastases free survival which may well lead to an improvement in overall survival with prolonged follow up.

The use of HS is now well accepted in all patients who undergo EBRT with or without HDR brachytherapy at our radiation oncology centres. However, the use of HS in patients undergoing LDR brachytherapy with or without EBRT is still being explored. Whilst there is value in proposing the use of HS in LDR brachytherapy patients who require EBRT, its use in patients who undergo LDR monotherapy alone is contentious. We will conduct a small prospective study to investigate the use of HS in LDR monotherapy. In addition, the use of extreme fractionation EBRT protocols (i.e. SBRT) is being investigated with multiple prospective and retrospective studies reporting comparable results to standard EBRT. Although the median follow up for the majority of studies have been short, the bRFS and late toxicity rates are acceptable. The use of extreme fractionation SBRT schedules has the potential of increasing late GI toxicity and the use of HS to prevent or minimise the risk will need to be investigated.

The use of HS also reduced the risk of grade 1 urinary incontinence. Overall, no difference in grade 2 or more GU toxicity was seen. In patients who undergo brachytherapy, the use of a pre-emptive mini TURP may be warranted to minimise the risk of urethral strictures and subsequent surgical interventions. The latter may lead to an increased risk of future urinary incontinence. In addition, we have also shown the value of image guidance in brachytherapy. Unfortunately, there is little on offer in our attempts to minimise GU toxicity but the use of newer technology such as the magnetic resonance imaging linac may play a future role.

As HS is predominantly water based, its visibility on CT scans can be somewhat challenging. As such, a planning MRI scan is usually performed to aid in the delineation of the implanted HS. We
have found that the HS can be visualised and delineated by varying the CT window level of a CT planning scan. However, the introduction of iodinated HS such as TraceIT will allow much easier visualisation of the implanted product due to its radiopaque properties. We have recently completed an ethics approved prospective study investigating the feasibility of TraceIT as a tissue expander in the intact prostate setting. The use of a planning MRI scan in the PPRT setting is recommended.

The use of HS in patients with macroscopic recurrences post-prostatectomy has allowed us to deliver ultra-high dose PPRT. Although we have demonstrated the feasibility of using HS as a tissue expander in patients with macroscopic recurrences post-prostatectomy, this is only a small case series. Longer follow up is required to confirm the low toxicity rates reported thus far. In addition, we will also be keenly observing their biochemical control. Our aim will be to perform a much larger prospective study to validate our results.

*Final Words*

The use of dose escalated RT for PC using IGRT, IMRT or brachytherapy has improved the results of prostate cancer treatment. The use of rectal spacers has minimized the risks of GI toxicity allowing for safer dose escalation. This will no doubt impact on the other OAR which is the bladder and potentially more GU toxicity may arise. Newer strategies to prevent or reduce GU toxicity will be called for in the future.
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Author/s: Chao, Michael Wan Tien

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