ORIGINAL ARTICLE

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

Michael Chao[1,2,3] · Daryl Lim Joon[2] · Vincent Khoo[2,4,5,6] · Nathan Lawrentschuk[2] · Huong Ho[1] · Sandra Spencer[1] · Yee Chan[2,3] · Alwin Tan[7] · Trung Pham[8] · Shomik Sengupta[2,9] · Kevin McMillan[3,9] · Madalena Liu[3] · George Koufogiannis[3] · Chee Wee Cham[7] · Farshad Foroudi[2] · Damien Bolton[2,3]

Abstract

Purpose 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

✉ Michael Chao
  Michael.Chao@genesiscare.com.au

1   Genesis Cancer Care Victoria, 36 Mt Dandenong Road, Ringwood East, VIC 3135, Australia

2   The Austin Hospital, Heidelberg, Australia

3   Ringwood Private Hospital, Ringwood East, Australia

4   University of Melbourne, Melbourne, Australia

5   Monash University, Melbourne, Australia

6   Royal Marsden Hospital, London, UK

7   The Bays Hospital, Mornington, Australia

8   The Valley Private Hospital, Mulgrave, Australia

9   The Box Hill Hospital, Box Hill, Australia

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
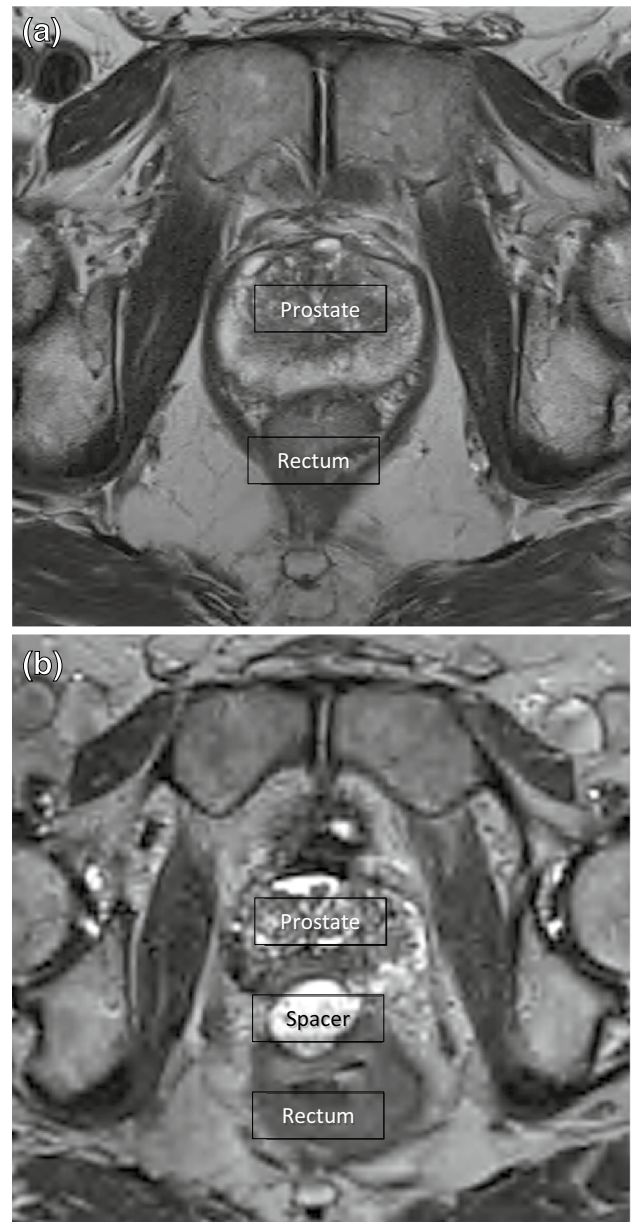

Fig. 1 T2-weighted magnetic resonance images (MRI) of a patient at baseline/pre-HS (**a**) and post-HS insertion (**b**). The HS is 90% water, therefore, has a hyperintense T2-weighted MRI signal
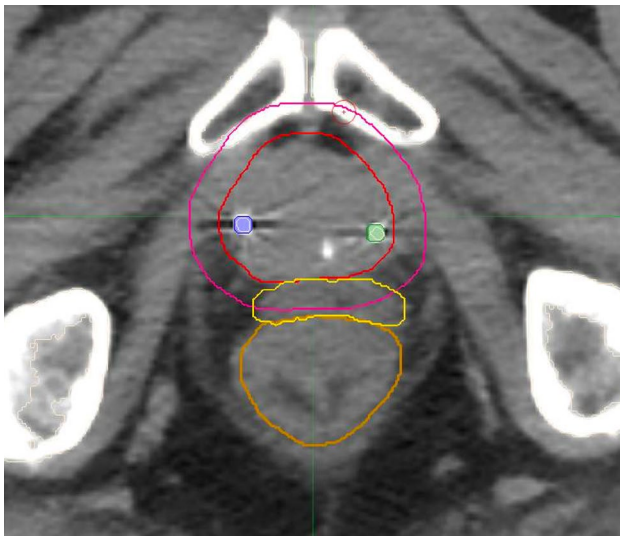
Fig. 2 Transverse computer tomographic scan images of prostate delineated in red, hydrogel spacer in yellow and rectum in brown. Gold seed fiducial markers in blue and green. The planning target volume for prostate receiving 78 Gy (PTV78) is delineated in pink and is situated outside the rectum

per fraction over 39 days, delivered to $\geq 95\%$ 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.

Table 1 Patient characteristics

Attribute	Study group
Age (years)	73.7 (range 61–84)
PSA (ng/ml)	2.5 (range 0.1–14.1)
T stages	
T1	4
T2	21
T3	6
Combined Gleason score	
6	3
7	22
8	3
9	3
NCCN risk grouping	
Low risk	3
Intermediate risk	19
High risk	9
ADT	
Yes	28
No	3

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

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 cm^3 vs 57.4 cm^3), mean rectal volumes (73.1 cm^3 vs 74.3 cm^3) and mean bladder volumes (291 cm^3 vs 357 cm^3).

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 1 patient (3.2%) with bowel frequency occurring at 6 months and resolving by 12 months post RT. There were no grade 2 or 3 acute or late GI 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 rV78 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 $\geq 25\%$, 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

Table 2 Pre-HS and post-HS rectal volume dosimetry (mean ± SD)

	rV50	rV60	rV70	rV75	rV78
Pre-HS	33 ± 2.7	20.9 ± 2.1	13.7 ± 1.6	8.6 ± 1.3	1.0 ± 0.4
Post-HS	26.4 ± 2.9	14.3 ± 2.1	8.0 ± 1.4	4.6 ± 1.1	0.8 ± 0.3
Relative reduction%	20.1	31.6	41.3	47.1	15.9
P value	< 0.001	< 0.001	< 0.001	< 0.001	0.55

rV volume of rectum receiving dose in Gray, *HS* hydrogel spacer

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.

Compliance with ethical standards

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