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Title: Prospective analysis of hydrogel spacer for prostate cancer patients undergoing radiotherapy

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Abstract

Objective: The purpose of this study was to report on the dosimetric benefits and late toxicity outcomes following injection of a hydrogel spacer (HS) between the prostate and rectum for patients treated with prostate radiotherapy.

Methods: A total of 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 peri-rectal space prior to intensity modulated radiation therapy (IMRT) or volumetric modulated radiation therapy (VMAT). Spacer safety, dosimetric benefits and the immediate to long-term effects of gastrointestinal toxicity (GI) were assessed.

Results: There were no postoperative complications reported. Mean prostate size were 66.0cc (25.0cc – 187.0cc). Rectal dose volume parameters were observed with volume of rectum receiving 70Gy (rV_{70}), 75Gy (rV_{75}) and 78Gy (rV_{78}) were 7.8%, 3.6% and 0.4%. 21% (16/76) developed acute grade 1 GI toxicities but all were resolved completely by 3 months post-treatment. 3% (2/76) developed late grade 1 GI toxicities. No patients experienced 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

Key words: hydrogel spacer; IMRT; VMAT; prostate cancer

Introduction

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

Although recent advances in RT delivery, including image guided RT (IGRT) and IMRT and VMAT have reduced toxicity rate, it has proven a challenge to spare the anterior rectal wall. A number of different methods such as collagen, hyaluronic acid and blood patch have been explored with minimal success rate[3,4,5,6]. HS implanted between the prostate and rectum in recent years has gained noticeable interest in increasing the peri-rectal spacing and reducing radiotherapy related rectal toxicity[7] either in external beam RT alone; low or high dose rate brachytherapy or combination of both external beam RT and brachytherapy[8,9].

The safety and efficacy of hydrogel in 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[12,13,14]. Therefore, this study aimed to report on our initial experience of using a HS implant for the treatment of prostate cancer.

Materials 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 prior to commencement. All participants provided written medical informed consent before undergoing any therapeutic procedure.

Participants

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

Hydrogel implant procedure

Under general anaesthesia and with transrectal ultrasound guidance, all patients underwent transperineal insertion of three intra-prostatic gold seed markers[7] followed by injection of 8-10 millimetres of 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 (RO) 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 implanted procedure was disseminated to the urologists by the RO to ensure a high quality insertion of HS[16].

Treatment planning

A pelvic computed tomography (CT) scan for IMRT/VMAT treatment planning was carried out within 5 days post 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) treatment planning system (TPS). Clinical target volumes(CTV) comprised of prostate and seminal vesicle and were defined in concordance with 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 V_{78}, V_{75}, V_{70}, V_{60} and V_{50} were 5%, 15%, 20%, 35% and 50% of the rectal volume, 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 1.0cm 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 magnetic resonance imaging (MRI) scan to aid with visualization of the hydrogel, in the event of any doubt in identifying the hydrogel it was contoured as rectum. Degree of separation achieved between the anterior rectal wall and the posterior edge of prostate was quantified at apex, mid-gland and base. Rectal V_{78}, V_{75}, V_{70}, V_{60} and V_{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 following 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 two-year period, with only one patient reported lost to follow up after completing his course of RT. Our population included men with a median age of 74 years (IQR 60 to 88 years) presenting with a median PSA of 10.4 (IQR 1.1 to117). Median follow-up was 14 months (IQR 12 to 29 months), with the last patient completing treatment in February 2016. For patient demographic and disease-specific variables, see Table 1.

Rectal spacing outcomes

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

Dosimetric outcomes

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

Toxicity outcomes

None of the patients reported any rectal bleeding. There were no reports of any adverse events including rectal perforation, or infection following hydrogel injection. 16 (21%) patients overall developed acute grade 1 GI toxicity with all symptoms resolved within three months after completion of treatment (Tab. 4). One patient developed a late grade 1 rectal haemorrhage at 9 months post treatment, however this was due to rectal haemorrhoids. One patient developed late grade 1 proctitis at eight months post 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 timepoints 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 post RT.

63 (83%) patients developed acute grade 1 GU toxicity. These symptoms persisted in 18 (24%) patients three months after completion of treatment. Two (3%) patients developed a urinary stricture requiring intermittent self-catheterisation (Tab. 5).

Discussion

Progress in radiotherapy techniques in recent years have allowed dose escalation with better PTV coverage, significantly improving treatment outcomes with reduced treatment associated GI toxicities. Our study demonstrated HS was well tolerated with no adverse effects associated with the device, 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 indicated that the application of HS has 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 results were in accordance with other published studies[12, 14, 18, 19] and this has further validated our findings. Due to a broad range in prostate size, we also investigated the clinical benefits of HS in larger prostate size. Our study confirmed rectal dosimetry parameters (Fig. 3) were consistent across the cohort, demonstrating it is possible to achieve noticeable reduction in rV_{70} irrespective of prostate size.

We recognise that our rV_{70} and V_{75} are marginally higher (Table 6) than other studies however we attribute this finding to our contouring method. In contrast to some studies[3, 14] where the rectum was contoured from the recto-sigmoid junction to the level of ischial tuberosity, our rectum was contoured from 1.0cm 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 high reduction in the high-dose regions was the logical explanation for our decreased patient reported GI toxicities. In particular, an overall of only 16 patients (20%) experience acute grade 1 GI toxicities, which resolved completely (97%) at 3 months post-treatment. The remaining two patients developed either late grade 1 rectal haemorrhage (n=1) or proctitis (n=1) at 8 months post-treatment. No patients experienced acute or late grade 2+ GI toxicities. Uhl[21] have observed similar

low-grade 1 GI toxicities at 12 months and no reported grade 2+ GI toxicities, whilst slightly higher acute and late GI toxicity rates were noted by Uhl[20] and Whalley[6].

Our work builds upon published studies examining the use of HS in our region[12, 13, 14, 22, 23, 24]. In particular, our findings are comparable to three studies[12, 13, 14] 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 (V65 to V82) range. More recently, a study by Mariados[18] examined 222 patients who were randomized with HS (n=149) or without HS (n=73) whilst undergoing IMRT to a dose of 79.2 Gy in 44 fractions. The authors have reported similar results to our study with no significant adverse events related to HS injection and no differences in rates of acute rectal toxicity between the HS and control groups. Another study by Pinkawa[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 have also reported similar findings to our study 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 study that has been listed below. Firstly, our study was 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 a HS for prostate radiotherapy[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 this study, we were quite confident with the level of consistency with the HS injection technique, degree of contouring and grading of toxicities. Finally, we did not have any restrictions placed on the prostate size (i.e. less than 80cc) compared to other published data[3, 17, 19, 20] which allowed analysis of the effectiveness of the hydrogel spacer in its ability to increase the peri rectal space, irrespective of prostate volume.

This study had a series of 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 were 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 hydrogel inserted. Lastly, we did not record patient-centred outcomes such as health-related or disease-specific quality of life.

In conclusion, although our study was limited in its scope, the data has provided 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.

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Table 1. Patient Characteristics

Demographics	Patient Number
Stage	
I	16% (12/76)
II	57% (43/76)
IIIa	27% (21/76)
ISUP	
1	24% (18/76)
2	36% (27/76)
3	13% (10/76)
4	8% (6/76)
5	19% (15/76)
PSA level (ng/mL)	
≤4	18% (14/76)
>4-10	51% (39/76)
≥10-20	21% (16/76)
≥20	10% (7/76)
Prostate Size	
<50 cc	38% (29/76)
50-100 cc	45% (34/76)
>100cc	17% (13/76)

Table2. Peri-rectal spacing results

Patient Cohort (n=76)	**Mean (±SD), mm**	**Median (Range), mm**	
Base	10.6 (±2.5)	11 (5-17)	
Mid Gland	7.7 (±2.1)	8 (4-12)	
Apex	4.9(±1.9)	5 (1-9)	
Different Prostate Size	<50cc (n=29)	>50cc (n=34)	>100cc (n=13)
Base			
Mean (±SD), mm	10 (±2.2)	11 (±2.5)	10.9 (±2.9)
Median (Range), mm	10 (5-14)	11 (6-17)	11 (7-15)
Mid-gland			
Mean (±SD), mm	7.4 (±1.5)	8.1 (±2.3)	8 (±2.2)
Median (Range), mm	7 (4-11)	8 (2-12)	8 (5-11)
Apex			
Mean (±SD), mm	5 (±1.4)	5.1 (±2.1)	4.5 (±2.1)
Median (Range), mm	5 (3-8)	5 (3-8)	5 (2-8)

Table 3. Achievable Rectal Dose Constraint for HS

OAR Constraints	Hydrogel Spacer Mean (%)
Rectum V50Gy≤50%	27.3
Rectum V60Gy≤35%	14.4
Rectum V70Gy≤20%	7.8
Rectum V75Gy≤15%	3.6
Rectum V78Gy≤5%	0.4

Table 4. Radiation induced GI toxicity

	Overall GI Toxicity	
	Acute (n=76)	**Late (n=75†)**
Grade 0	60 (79%)	73 (97%)
Grade 1	16 (21%)	2 (3%)
Grade 2+	0	0

†1 patient lost to follow up

Table 5. Radiation induced GU toxicity

	GU Toxicity	
	Acute (n=76)	**Late (n=75†)**
Grade 0	13 (17%)	57 (76%)
Grade 1	63 (83%)	16 (21%)
Grade 2+	0	2 (3%)

†1 patient lost to follow up

Table 6. Mean ± SD comparing rectal dose volume

Study groups	rV70	rV75
Our cohort (n=76)	8.5±4.2	4±2.5
Mariados (n=148)	3.3±3.2	0.6±0.9[€]
Song (n=45)	5.1±4.2	1.2±1.3

[€] rV80

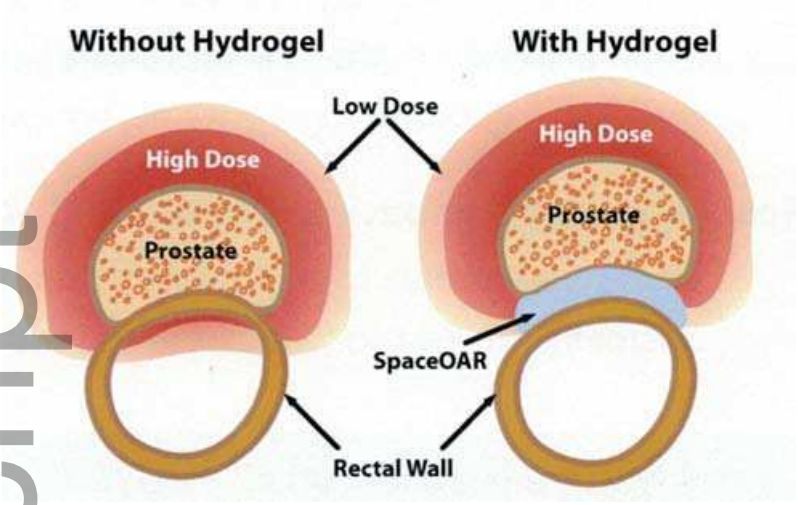
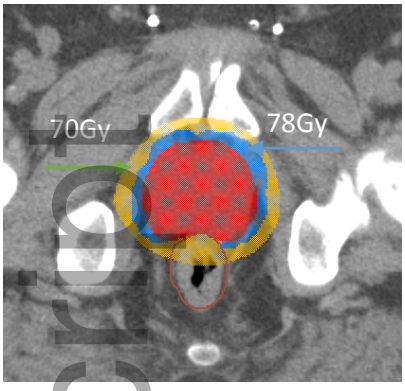
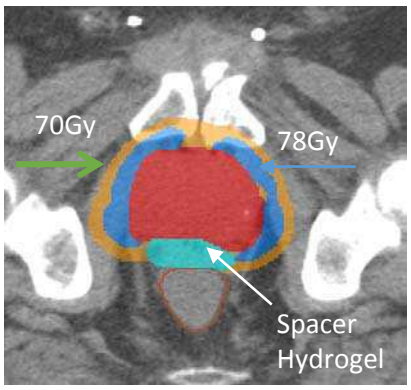


Fig 1. Insertion of HS into the peri-rectal space pushing the rectum out of the high dose region.

Figure 2. HS injection pushing the rectum out of the field significantly reduced the rectal dose



Pre Spacer Injection Axial



Post Spacer Injection Axial

Figure 3. Mean rectal volume constraints (cc) for different prostate size

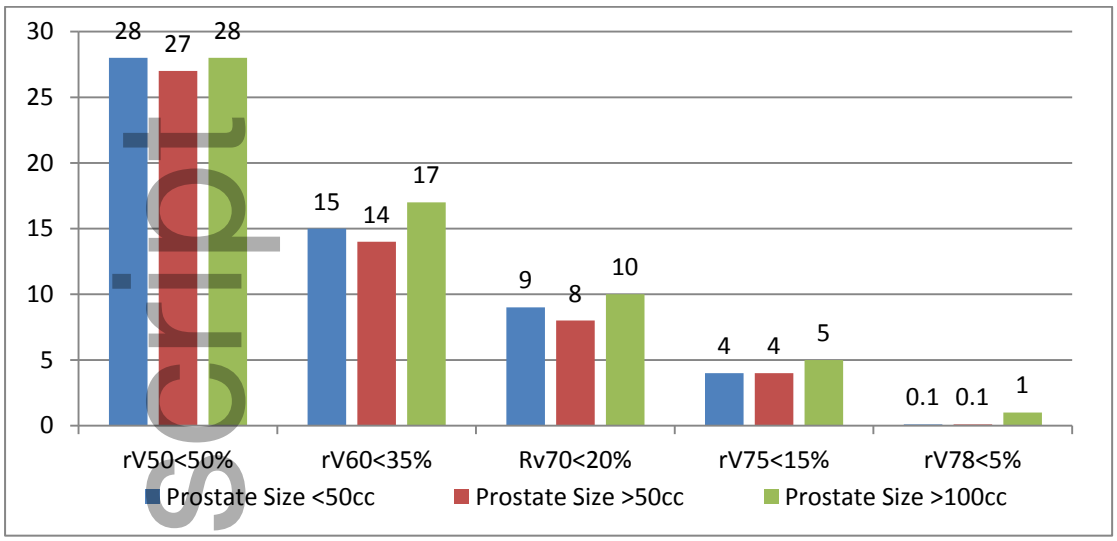


Figure 4. Acute GI toxicity by timepoint