Original paper

Impact of hydrogel and hyaluronic acid rectal spacer on rectal dosimetry and toxicity in low-dose-rate prostate brachytherapy: a multi-institutional analysis of patients' outcomes

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Abstract

Purpose: To report on rectal dosimetry and toxicity outcomes in men with prostate cancer (PCa) treated with iodine-125 low-dose-rate brachytherapy (LDR-BT) with or without polyethylene glycol hydrogel (HS) or hyaluronic acid (HA) rectal spacer (RS) insertion.

Material and methods: Seventy consecutive men treated with LDR-BT between December 2017 and July 2019 were included in this study, including twenty-eight (40%) men who had RS insertion according to the preference of referring urologist, compared to a group of forty-two men (60%) without RS. Descriptive statistics were used to compare RS safety, dosimetric effects on organs at risk (rectum and urethra), and gastrointestinal (GI) and genitourinary toxicities (GU) (assessed using the CTCAE v.4) between the two groups of patients.

Results: The median prostate-rectal separation with RS at mid prostate was 10 mm (IQR, 8-11.5 mm). The median follow-up was 23.5 months. There were no post-operative complications for RS insertion. There was significantly reduced rectal dosimetry in RS-group vs. non-RS group; the median RV_{100} was 0.0 cc (IQR, 0.0-0.0 cc) vs. 0.4 cc (IQR, 0.1-1.1 cc) ($p < 0.001$), respectively. The mean rectal D_{1cc} and D_{2cc} were 52.4% vs. 84.2% ($p < 0.001$) and 45.7% vs. 70.0% ($p < 0.001$) for RS and non-RS group, respectively. There were no statistically significant differences in the mean urethral D_{20}, D_5, and D_1. There were significantly less grade 1 acute and late GI toxicities in RS-group when compared to non-RS group (0% vs. 24%, $p = 0.004$ for acute GI toxicity; 4% vs. 33%, $p = 0.003$ for late GI toxicity). There were no reported acute or late grade 2 or above GI toxicities.

Conclusions: Insertion of RS in men treated with LDR-BT is safe and resulted in a significant reduction in rectal dosimetry. The reduction in rectal dosimetry with RS insertion translates into significantly reduced acute and late GI toxicities.

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Key words: low-dose-rate brachytherapy, prostate cancer, rectal spacer, rectal toxicity, rectal dosimetry.

Purpose

Low-dose-rate brachytherapy (LDR-BT) is an effective curative treatment for low- and intermediate-risk localized prostate cancer (PCa) [1], and as salvage radiotherapy with curative intent in localized recurrence [2]. However, the risk of rectal toxicities poses a major challenge to prostate irradiation. This was demonstrated in a large retrospective study, which reported an incidence of 20.57% grade 1 proctitis and 6.4% grade 2 proctitis, following individual or combination BT [3]. Significantly, von Gellekom *et al*. demonstrated a correlation between increasing

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rectal D_{2cc} with an increasing incidence of rectal toxicity [4]. Snyder *et al*. also reported a reduced rate of ≥ grade 2 rectal toxicity, if V_{100} to the rectum was minimized to < 1.3 cc [5]. Peters *et al*. further recommended minimizing D_{2cc} to less than 100 Gy in whole gland salvage iodine-125 (^{125}I) BT prostate permanent implant to minimize severe gastrointestinal (GI) toxicities [6]. Furthermore, Veccia *et al*. demonstrated that reducing post-LDR-BT implant rectal V_{100} (RV_{100}) to ≤ 0.5 cc, yielded improved acute and chronic rectal function and patient's quality of life [7]. All current literature demonstrated a need to minimize both rectal dose and rectal volume receiving maximum irradiation in order to avoid severe GI complications.

The use of a bio-degradable recto-prostatic spacer has been widely studied over the past decade and examining its' utility to increase the distance between prostate and rectum and thus, minimizing radiation dose received by the rectum. Currently available options for recto-prostatic spacer include hyaluronic acid (HA), implanted balloons [8], collagen implants [9], and polyethylene glycol hydrogel (HS). Hyaluronic acid, HS, and bio-degradable implanted balloons all demonstrated promising preliminary results in reducing rectal dosimetry [10-13] and decreasing rates of acute and chronic rectal toxicities [14, 15].

Both HS and HA rectal spacers present as cost-effective [16], safe, and effective recto-prostatic spacers. Current evidence suggests a significant reduction in radiation dose to the rectum in HS patients undergoing LDR-BT with or without external beam radiotherapy (EBRT), when compared to patients without hydrogel injection [17-20]. Furthermore, HS is associated with minimal post-operative complications and low rates of grade ≥ 3 acute or late rectal toxicities [13, 21-25]. Despite the promising findings from the literature, there have been a lack of large scale prospective clinical trials conducted for HS or HA rectal spacers in LDR-BT. As a result, this retrospective multi-institutional cohort study aims to report the rectal dosimetry and toxicity outcomes in men with PCa treated with LDR-BT with or without HS or HA rectal spacer (RS) insertion.

Material and methods

Study design, setting, and ethics

This retrospective case-control cohort study, assessing a prospective database, was performed to evaluate the efficacy and safety of HS or HA RS in LDR-BT for patients with clinically localized low-risk and intermediate-risk PCa at a private radiation oncology center (Genesis Care) in Melbourne, Australia. Ethics approval was sourced from the above institution on March 5, 2018. Between October 2017 and July 2019, 70 consecutive patients were enrolled into this study. LDR-BT prescription was 145 Gy modified peripherally loading (MPD) using ^{125}I as monotherapy or with downsizing androgen deprivation therapy (ADT). The use of HS or HA RS was based on the preference of treating physician (i.e., urologist) only. HS RS (SpaceOAR®, Boston Scientific, MA, USA) was exclusively used for insertion prior to 2020, whilst HA RS (Barrigel®, Palette Life Sciences, Stockholm Sweden) was preferred following 2020, as it became commercially available in Australia.

All patients were initially assessed with a thorough medical history, examination, and serum prostate specific antigen (PSA) level. A digital rectal examination (DRE) was performed to evaluate patient's clinical T-stage (cT). Transperineal ultrasound-guided biopsy (TPUS) was performed and assessed by an accredited general pathologist to produce pathological staging with either Gleason score or International Society of Urological Pathology (ISUP) score. All patients with Gleason score > 7 was staged with computerized tomography (CT) scan of abdomen and pelvis, magnetic resonance imaging (MRI) prostate, and/or whole-body bone scan (WBBS).

Prostate cancer stratification was calculated based on D'Amico classification [26]. Low-risk PCa was defined as Gleason score ≤ 6, PSA ≤ 10 ng/ml, and stage cT1-cT2a; favorable and unfavorable intermediate-risk PCa were defined as Gleason score of 7 (favorable intermediate-risk group was defined as Gleason 3+4 grade group 2, whilst unfavorable risk group was defined as Gleason 4+3 grade group 3), and/or stage cT2b PCa. Patients without a specified cT2 sub-stage but with Gleason score ≤ 6 and PSA < 10, were reclassified as low-risk rather than left unclassified.

Gastrointestinal and genitourinary (GU) toxicities were assessed using common terminology criteria for adverse events (CTCAE) version 4.0. Acute GI and GU toxicities were defined as symptom occurrence within 3 months post-treatment, whilst late toxicities were described as symptom occurrence after 3 months post-treatment. Immediate or delayed post-operative complications following RS insertion, including, but not limited to, rectal tear, rectal perforation, rectal ulceration, rectal bleeding, infection, allergic reactions, and urinary retention were recorded in electronic medical records and/or on patient's progress note at their first post-treatment follow-up with radiation oncologist. Assessing physicians were not blinded to the use of RS.

Planning and treatment

This study implemented the same volume study, treatment planning, and treatment techniques as previously reported by Chao *et al*. [27].

Any patient who underwent a pre-implant TURP had limited resection with only 3-5 grams of tissue removed. If an intravesical median lobe was present, the lobe was resected down to prostatic capsule. In some cases, patients also had a transurethral incision of the prostate (TUIP). Patients did not proceed to their implant until at least 3 months after their TURP, with urodynamic tests and cystoscopy performed to confirm resolution of outlet obstruction and urethral healing.

Rectal spacer insertion with either HS (SpaceOAR®, Boston Scientific, MA, USA) or HA (Barrigel®, Palette Life Sciences, Stockholm, Sweden) was performed at the end of an implant via transrectal ultrasound guidance by the treating radiation oncologist or urologist. 10 cc of SpaceOAR© hydrogel spacer, or 9 cc of Barrigel© hyaluronic acid gel was introduced into the recto-prostatic space. RS insertion was performed at the end of the implant, as the

use of RS could degrade the images of the prostate, therefore interfere with the implant of brachytherapy rods. It could also potentially elevate the prostate anteriorly and cause pubic arch obstruction.

Patients were admitted overnight with an indwelling catheter (IDC) and discharged after a successful trial of void in the following morning. All patients attended a follow-up with the urologist at 2 weeks post-implantation as well as a follow-up with the radiation oncologist at 4 weeks post-implantation for post-implant dosimetry using CT/MRI to verify for post-procedural complications. Placement of RS and the resultant prostate-rectum separation was characterized using MRI.

The patients were then followed-up every 3 to 4 months for the first year by the treating radiation oncologist, and every 6 months for the next 5 years. PSA testing was performed for at least first 4 years of follow-up, with biochemical failure defined as PSA nadir + 2 ng/l, following implant and exclusion of PSA bounce according to Phoenix definition [28].

Statistical analyses

Descriptive statistics were performed to evaluate characteristics of the patients demographics, disease, treatment features, and post-treatment toxicities, and test for differences between groups. Continuous variables were presented as mean ± standard deviation or median (interquartile range) for normal and non-normal variables, respectively, using Student's *t*-test and Mann-Whitney test for differences between the two groups. Categorical variables were presented as counts and percentage frequencies, with chi-square or Fisher's exact test applied to evaluate differences in distribution between the groups. Analysis of the association between RV_{100} with acute and late GI toxicities included categorizing RV_{100} based on thresholds of ≤ 0.5, > 0.5, ≤ 1.3, and > 1.3 as per previously published dose constraints [5, 7, 29, 30]. Evaluations of association between pre- and post-implant rectal D_{1cc} and D_{2cc} relations with GI toxicities included consideration of medians and/or thresholds, as determined by utilization of receiver operating curve (ROC) analysis. Potential confounding effects of RV_{100}, D_{1cc}, and D_{2cc} values on the association between RS and late GI toxicity was explored using multi-variable logistic regression analysis. Multi-variable analysis could not be explored for acute GI toxicity due to no acute GI toxicity events in the RS cohort. Statistical analysis was conducted using Stata version 15.1 (StataCorp, College Station, Texas, USA), with statistical significance defined as p-value < 0.05.

Results

Patients' characteristics

The mean age of the study population was 66.1 years (SD = 6.8) (Table 1). Of the 70 men enrolled in the study, 28 patients (40%) received RS insertion and 42 men (60%) did not receive RS. The median follow-up was 23.5 months (IQR = 20.75 months). It was 26.5 months (IQR = 17.5 months) for the patients who did not receive RS, and 13 months (IQR = 20.5 months) for the patients who received RS. There were 19 men (27%) with low-risk PCa, 49 (70%) with favorable intermediate-risk PCa, and 3 cases (4%) with unfavorable intermediate-risk PCa, with a statistically significant difference in cT-stages in patients with RS vs. patients without RS insertion (p = 0.025). Overall, 43 men (61%) underwent TURP prior to LDR-BT, whilst 9 men (13%) received downsizing ADT, with no statistically significant differences between the cohorts. The high volume of TURP was attributed to poor urinary flow and was performed at the discretion of the treating urologist with small volume resection (3-5 grams of tissues removed) for patients with poor flow.

There was no statistically significant difference in the mean pre-radiotherapy (RT) PSA in patients treated with RS vs. non-RS group (5.0, SD = 2.6; 4.9, SD = 2.4; p = 0.91), or distribution in Gleason score (p = 0.53) or ISUP grading (p = 0.53).

There was no statistically significant difference in the number of patients treated with RS vs. patients not treated with RS (staging scan performed for almost all patients), who underwent MRI imaging (p = 0.64), CT staging (p = 1.00), WBBS (p = 1.00), or downsizing androgen deprivation therapy (ADT) (p = 1.00).

No PSA relapse was recorded in any men. The median follow-up PSA was 0.3 (IQR, 0.1-0.6) for men treated without RS, and 0.6 (IQR, 0.3-1.0) for men treated with RS (p = 0.019).

Dosimetry results

The mean prostate volume was 37.7 cc (SD = 9.1) (Table 2), with no statistically significant difference in the mean prostate volume recorded between men with RS vs. men without RS (p = 0.15; Table 2). The mean number of seeds inserted was 70.7 (SD = 7.9), with no differences between men with RS vs. men without RS (p = 0.42). No post-procedural insertion complications were recorded.

No statistically significant difference was recorded for the mean urethral D_{20}, D_5, and D_1 for men without RS insertion vs. men with RS insertion: 130.8% vs. 129.4% (p = 0.20), 137.1% vs. 135.5% (p = 0.22), and 145.0% vs. 141.5% (p = 0.061), respectively. Similarly, no statistically significant difference was recorded amongst the two groups for pre-RS insertion prostate D_{90}, V_{100}, V_{150}, and V_{200}, with 119.6% vs. 119.4% (p = 0.62), 98.6% vs. 98.6% (p = 0.42), 55.5% vs. 55.4% (p = 0.90), and 23.1% vs. 22.7% (p = 0.48), respectively, as well as for post-RS insertion prostate D_{90}, V_{100}, V_{150}, and V_{200}, with 98.5% vs. 99.6% (p = 0.66), 88.6% vs. 88.7% (p = 0.93), 50.3% vs. 48.9% (p = 0.58), and 23.6% vs. 22.0% (p = 0.61), respectively.

The median recto-prostatic separation, as measured from midline of the prostate, was 10 mm (IQR = 3.25 mm) in the patients who underwent RS. There was significantly reduced rectal dosimetry in men with RS vs. men without RS, i.e., RV_{100} = 0 cc (IQR = 0-0.0 cc) vs. RV_{100} = 0.4 cc (IQR = 0.1-1.1 cc), p < 0.001. Also, there was significantly reduced D_{1cc} and D_{2cc} in men with RS vs. men without RS. D_{1cc} in men with RS was 52.4% vs. 84.2% in men without RS (p < 0.001). D_{2cc} was 45.7% in men with RS vs. 70.0% in men without RS (p < 0.001).

Table 1. Patients' characteristics (overall, RS vs. non-RS group)

Factor	Overall	Patients without RS	Patients with RS	*p*-value
n	70	42	28	
Age, mean (SD)	66.1 (6.8) (*n* = 69)	66.9 (7.0)	64.9 (6.3) (*n* = 27)	0.25
Follow-up (months), median (IQR)	23.5 (20.75)	26.5 (17.5)	13 (20.5)	
Pre-RT PSA, mean (SD)	5.0 (2.5)	5.0 (2.6)	4.9 (2.4)	0.91
cT stage, *n* (%)				0.025
T1c	19 (27)	7 (17)	12 (43)	
T2a	49 (70)	34 (81)	15 (54)	
T2b	2 (3)	1 (2)	1 (4)	
Gleason score, *n* (%)				0.53
3+3	25 (36)	14 (33)	11 (39)	
3+4	42 (60)	27 (64)	15 (54)	
4+3	3 (4)	1 (2)	2 (7)	
ISUP, *n* (%)				0.53
1	25 (36)	14 (33)	11 (39)	
2	42 (60)	27 (64)	15 (54)	
3	3 (4)	1 (2)	2 (7)	
Cores positive, mean (SD)	0.3 (0.2)	0.2 (0.2)	0.3 (0.2)	0.030
Risk classification, *n* (%)				0.44
Low	24 (34)	13 (31)	11 (39)	
Favorable IR	43 (61)	28 (67)	15 (54)	
Unfavorable IR	3 (4)	1 (2)	2 (7)	
TURP, *n* (%)	43 (61)	29 (69)	14 (50)	0.14
MRI, *n* (%)	65 (93)	38 (90)	27 (96)	0.64
Downsizing ADT, *n* (%)	9 (13)	6 (14)	3 (11)	1.00
PSA relapse				
No	42 (100%)	28 (100%)		
PSA, median (IQR)	0.3 (0.1, 0.6) (*n* = 42)	0.6 (0.3, 1.0) (*n* = 28)	0.019	

Immediate and late GI and GU toxicities

There was a statistically significant difference in acute GI toxicity of 24% to 0% ($p = 0.004$) and in late GI toxicity of 33% to 4% ($p = 0.003$) in the non-RS vs. RS cohorts (Table 3). The only late GI toxicity in the RS cohort was observed in one patient with rectal bleeding. As shown in Table 3, the most common late GI toxicities observed in the non-RS cohort were grade 1 diarrhea, proctitis, and rectal bleeding. No acute or late grade 2 or higher GI toxicities were observed in either group.

Table 4 demonstrates further analyses of the association between RV_{100}, D_{1cc}, and D_{2cc} with acute and late GI toxicities. There was a statistically significant difference observed between patients with post-implant $RV_{100} \leq 0.5$ and > 0.5 and late GI toxicity (15% vs. 39%, $p = 0.049$). As there were no pre-implant RV_{100} values beyond 1.3, no assessment of association with acute GI toxicity could be performed. Rates of acute GI toxicity were higher in post-implant RV_{100} values > 1.3 compared to ≤ 1.3 (29% vs. 13%) and for late GI toxicity (29% vs. 21%), but neither comparison was statistically significant ($p = 0.26$ and 0.64, respectively).

Based on ROC analysis, acute GI toxicity was higher for patients with post-implant rectal D_{1cc} values > 67.45 (25% vs. 3%, $p = 0.014$), with late GI toxicity also higher (36% vs. 6%, $p = 0.003$). Similarly, acute GI toxicity rates were higher for post-implant rectal D_{2cc} values > 53.89 (23% vs. 3%, $p = 0.035$), with a cut-point > 54.81 maximizing the differential in late GI toxicity (35% vs. 6%, $p = 0.003$).

Univariate logistic regression analysis provided odds ratio of 0.07 (95% CI: 0.01-0.60%, $p = 0.15$) for log odds of late GI toxicity in the RS cohort, when compared to the non-RS cohort. After adjusting for post-implant RV_{100} > 0.5, statistical significance was maintained with a slightly higher odds ratio (OR = 0.09; 95% CI: 0.01-0.80%; $p = 0.030$). When adjusting for post-rectal D_{1cc} and D_{2cc} in separate models, statistical significance was not retained. Although, ORs were all in the order of < 0.2 (D_{1cc}: OR = 0.19, 95% CI: 0.01-2.70%, $p = 0.22$; D_{2cc}: OR = 0.16, 95% CI: 0.01-1.80%, $p = 0.14$), indicating that the association between RS and late GI toxicity was only marginally affected by confounding, and a strong association between RS and late GI toxicity remained.

Table 2. Pre- and post-RS implantation dosimetric findings

Pre-implant													
Factor	Pre-prostate D_{90} (%), mean (SD)	Pre-prostate V_{100} (%), mean (SD)	Pre-prostate V_{150} (%), mean (SD)	Pre-prostate V_{200} (%), mean (SD)	Pre-RV_{100} (cc), median (IQR)	Pre-rectal D_{1cc} (%), mean (SD)	Pre-rectal D_{2cc} (%), mean (SD)	US prostate volume cc, mean (SD)	Seeds, mean (SD)	Activity (U), median (IQR)	Urethra D_{20} (%), mean (SD)	Urethra D_5 (%), mean (SD)	Urethra D_1 (%), mean (SD)
Overall	119.5 (1.7)	98.6 (0.3)	55.4 (2.9)	22.9 (2.0)	0.1 (0.1, 0.2)	86.1 (4.1) (n = 69)	77.0 (4.3)	32.0 (7.8)	70.7 (7.9)	0.5 (0.5, 0.6)	130.2 (4.7)	136.5 (5.3)	143.6 (7.6)
Patients with RS	119.4 (1.6)	98.6 (0.3)	55.4 (2.3)	22.7 (2.1)	0.1 (0.1, 0.2)	86.6 (3.5)	77.4 (4.2)	33.7 (8.1)	71.6 (8.9)	0.5 (0.5, 0.6)	129.4 (4.7)	135.5 (6.1)	141.5 (8.3)
Patients without RS	119.6 (1.8)	98.6 (0.3)	55.5 (3.2)	23.1 (1.9)	0.2 (0.1, 0.3)	85.8 (4.5) (n = 41)	76.8 (4.5)	30.9 (7.4)	70.0 (7.3)	0.5 (0.5, 0.6)	130.8 (4.6)	137.1 (4.8)	145.0 (6.9)
p-value	0.62	0.42	0.90	0.48	0.36	0.43	0.62	0.13	0.42	0.49	0.20	0.22	0.061

Post-implant									
Factor	Post-prostate D_{90} (%), mean (SD)	Post-prostate V_{100} (%), mean (SD)	Post-prostate V_{150} (%), mean (SD)	Post-prostate V_{200} (%), median (IQR)	Post-RV_{100} (cc), median (IQR)	Post-rectal D_{1cc} (%), mean (SD)	Post-rectal D_{2cc} (%), mean (SD)	CT prostate volume cc, mean (SD)	RS distance minimum (mm), median (IQR)
Overall	98.9 (10.4)	88.6 (6.2)	49.8 (10.6)	22.9 (18.2, 29.0)	0.1 (0.0, 0.5)	71.5 (22.9)	60.3 (18.6)	37.7 (9.1)	10.0 (3.25) (n = 28)
Patients with RS	99.6 (10.1)	88.7 (6.6)	48.9 (9.9)	22.0 (18.1, 29.1)	0.0 (0.0, 0.0)	52.4 (9.5)	45.7 (9.4)	39.6 (10.1)	10.0 (3.25) (n = 28)
Patients without RS	98.5 (10.8)	88.6 (6.0)	50.3 (11.1)	23.6 (18.2, 28.4)	0.4 (0.1, 1.1)	84.2 (20.2)	70.0 (16.9)	36.5 (8.2)	N.A.
p-value	0.66	0.93	0.58	0.61	< 0.001	< 0.001	< 0.001	0.15	–

N.A. – not available or collected, SD – standard deviation, IQR – interquartile range

Table 3. Acute and late GU and GI toxicities in patients treated with RS vs. no RS

Toxicity type and grade	Patients without RS (n = 42)	Patients with RS (n = 28)	p-value
Acute toxicities, *n* (%)			
Any GU toxicity	37 (88)	24 (86)	1.00
Any grade 2+ GU toxicity	2 (5)	1 (4)	0.81
Any GI toxicity	10 (24)	0 (0)	0.004
Any grade 2+ GI toxicity	0 (0)	0 (0)	1.00
Late toxicities, *n* (%)			
Any late GU toxicity	27 (64)	18 (64)	1.00
Any grade 2+ GU toxicity	4 (10)	1 (4)	0.64
Any late GI toxicity	14 (33)	1 (4)	0.003
Any grade 2+ GI toxicity	0 (0)	0 (0)	1.00

Table 4. Dosimetric association with acute and late toxicities

Variable	Acute GI toxicity			Late GI toxicity		
	No	Yes	p-value	No	Yes	p-value
Group			0.004			0.003
Non-RS cohort	32 (76.2)	10 (23.8)		28 (66.7)	14 (33.3)	
RS cohort	28 (100.0)	0 (0)		27 (96.4)	1 (3.6)	
Pre-RV_{100} (cc)			0.146			0.58
≤ 0.5	57 (87.7)	8 (12.3)		50 (76.9)	15 (23.1)	
> 0.5	3 (60.0)	2 (40.0)		5 (100.0)	0	
Pre-RV_{100} (cc)						
≤ 1.3	60 (85.7)	10 (14.3)		55 (78.6)	15 (21.4)	
> 1.3	0 (0)	0 (0)		0 (0)	0 (0)	
Pre-rectal D_{1cc} (%)			0.74			0.77
≤ 86.60 (median and ROC)	31 (83.8)	6 (16.2)		30 (81.1)	7 (18.9)	
> 86.60 (median and ROC)	29 (87.9)	4 (12.1)		25 (75.8)	8 (24.2)	
Pre-rectal D_{2cc} (%)			0.18			0.39
≤ 77.08 (median and ROC)	33 (91.7)	3 (8.3)		30 (83.3)	6 (16.7)	
> 77.08 (median and ROC)	27 (79.4)	7 (20.6)		25 (73.5)	9 (26.5)	
Post-RV_{100} (cc)			0.71			0.049
≤ 0.5	45 (86.5)	7 (13.5)		44 (84.6)	8 (15.4)	
> 0.5	15 (83.3)	3 (16.7)		11 (61.1)	7 (38.9)	
Post-RV_{100} (cc)			0.26			0.64
≤ 1.3	55 (87.3)	8 (12.7)		50 (79.4)	13 (20.6)	
> 1.3	5 (71.4)	2 (28.6)		5 (71.4)	2 (28.6)	
Post-rectal D_{1cc} (%)			0.014			0.003
≤ 67.45 (ROC)	33 (97.1)	1 (2.9)		32 (94.1)	2 (5.9)	
> 67.45 (ROC)	27 (75.0)	9 (25.0)		23 (63.9)	13 (36.1)	
Post-rectal D_{2cc} (%)			0.035			
≤ 53.89 (ROC)	30 (96.8)	1 (3.2)				
> 53.89 (ROC)	30 (76.9)	9 (23.1)				
Post-rectal D_{2cc} (%)						0.003
≤ 54.81 (ROC)				31 (93.9)	2 (6.1)	
> 54.81 (ROC)				24 (64.9)	13 (35.1)	

ROC – cut-point as defined by receiver operating curve (ROC) analysis

Discussion

Safety analyses

This retrospective multi-institutional study demonstrated that RS insertion with HA or HS spacers were safe, with no post-operative complications identified. This remained consistent with safety analysis performed by Heikkilä *et al*. and Prada *et al*. for HS and HA spacer injections, respectively, with both studies showing no post-operative complications [17, 31]. Furthermore, a systematic review performed by Miller *et al*. showed a 97% success rate with HS insertion and a low rate of procedural complication (0-10% of patients), which were mild and transient in nature [32].

RS distance

The median distance of separation achieved in this cohort remained consistent to that reported in the literature. Similar recto-prostatic separations were described in intensity-modulated radiation therapy (IMRT) [19], LDR-BT, and HDR-BT using either HS or HA insertions [14, 21, 22, 33]. Significantly two systematic reviews have established similar prostate-rectum separation with HS insertion in EBRT, BT, and combination RT (11.2 mm) [32] as well as in LDR-BT and HDR-BT (10 mm) with that of the current study [25].

Dosimetry outcomes

The present study showed comparable prostate and urethral dosimetry measures for the cohort treated with RS and that not treated with RS. The post-implant constraints and dose goals were consistent with guidelines laid out by the American Association of Physicists in Medicine (AAPM) and the American Brachytherapy Society [29, 34]. Most significantly, rectal dosimetry measures were significantly reduced in the RS cohort when compared to the non-RS cohort. As outlined above, there was a significant reduction in RV_{100} post-RS insertion (0.4 cc in the non-RS cohort vs. 0.0 cc in the RS cohort; $p < 0.001$). The mean rectal D_{1cc} and D_{2cc} were both significantly reduced in patients with RS compared to the non-RS cohort (52.4% vs. 84.2% for D_{1cc}, and 45.7% vs. 70.0% for D_{2cc}; $p < 0.001$).

Reduced rectal dosimetry following RS insertion was widely reported in high-dose-rate brachytherapy (HDR-BT), including Chao *et al*. study, who demonstrated reduced rectal dose volumes from rectal V_{30} to rectal V_{80} following HS insertion [33,35]. Strom *et al*. observed that HS insertion in patients treated with HDR-BT with or without IMRT, demonstrated significantly reduced mean rectal D2 ml (47 ±9%) when compared to those without HS insertion (60 ±8%), with values similar to those reported in this study [36]. Significantly, Taggar *et al*. showed reduced D_{1cc} and D_{2cc} values for HS insertion in patients treated with LDR-BT with palladium-103 as monotherapy, with EBRT, or as salvage monotherapy, when compared to patients not treated with HS [13]. HA insertion was demonstrated to reduce rectal dosimetry in HDR-BT with EBRT and HDR-BT in gynecological cancers [31, 38]. In the setting of IMRT, a phase 3 multicenter randomized clinical trial has been performed with HS insertion, yielding a significant reduction in rectal V_{70} post-spacer insertion [39-41]. Another clinical trial by van Gysen *et al*. was demonstrated a significant reduction in rectal doses (V_{30} to V_{80}) post-HS insertion in 10 patients treated with volumetric modulated arc therapy (VMAT) [42]. These findings suggest that HS insertion produces a consistent reduction in rectal dosimetry across different radiotherapy settings.

Placement of HS in patients treated with ^{125}I LDR-BT was demonstrated by Morita *et al*., showing reduced RV_{150} and RV_{100} compared with those not treated with HS [43]. Furthermore, a systematic review, which included 12 studies of HS insertion in the setting of LDR-BT and HDR-BT with or without EBRT, VMAT, or IMRT demonstrated that rectal doses were reduced across all these different settings [25]. Further studies by Kahn *et al*., Butler *et al*., Patel *et al*., Taggar *et al*., Zhang *et al*., and Liu *et al*. all showed improvements in rectal dosimetry post-HS insertion for patients treated with LDR-BT with or without EBRT [13, 44-49]. As such, the reduced rectal dosimetry post-RS insertion in the present study were comparable to, and reaffirming findings from, current literature on LDR-BT.

Table 5. Multi-variable analyses

Multi-variable, adjusted for post-RV_{100} (cc) > 0.5			
Variable	Late GI toxicity		
	OR	95% CI	*p*-value
Group			
Non-RS cohort	1.00		
RS cohort	0.09	0.01% to 0.80%	0.03
Post-RV_{100} (cc)			
≤ 0.5	1.00		
> 0.5	1.55	0.42% to 5.63%	0.51
Multi-variable, adjusted for rectal D_{1cc} (%) > 67.45			
Variable	Late GI toxicity		
	OR	95% CI	*p*-value
Group			
Non-RS cohort	1.00		
RS cohort	0.19	0.01% to 2.70%	0.22
Post-rectal D_{1cc} (%)			
≤ 67.45	1.00		
> 67.45	3.14	0.40% to 24.45%	0.28
Multi-variable, adjusted for rectal D_{2cc} (%) > 54.81			
Variable	Late GI toxicity		
	OR	95% CI	*p*-value
Group			
Non-RS cohort	1.00		
RS cohort	0.16	0.01% to 1.80%	0.14
Post-rectal D_{2cc} (%)			
≤ 54.81	1.00		
> 54.81	3.19	0.50% to 20.34%	0.22

OR – odds ratio

Toxicity outcomes

There was no statistically significant difference in acute or late grade 1 to 3 GU toxicities between the RS group and the non-RS group (Table 3). No acute or late grade 4 GU toxicities were recorded in this study. Similar incidence of GU toxicities were reported by Uhl *et al*., where HS cohort experienced 41.7% acute grade 1, 35.4% grade 2, and 2.1% grade 3 GU toxicities, and 17% late grade 1 and 2.1% late grade 2 GU toxicities [50]. Chao *et al*. reported no statistically significant difference in acute or late GU toxicities between group treated with HS and group not treated with HS in HDR-BT with or without EBRT [33]. This study showed that RS insertion did not increase the incidence of acute or late ≥ grade 1 GU toxicities, with reported incidences comparable to the current literature.

The present study demonstrated a statistically significant reduction in acute and late GI toxicities post-RS insertion, which were supported by findings of the literature. Wilder *et al*. showed that HA insertion yielded an incidence of 0% acute grade 1 to 3 acute diarrhea in 10 treated patients following IMRT and HDR-BT, when compared to an incidence of 29.7% in patients who did not receive HA [51]. Taggar *et al*. reported an incidence of 9.5% grade 1 rectal discomfort or rectal bleeding post-HS insertion for LDR-BT with or without EBRT [13]. A systematic review performed by Vaggers *et al*. on HS use in prostate brachytherapy described an acute grade 1 or 2 GI toxicity rate of 33.7% and a low-rate of grade 3 or 4 GI complications (0.22%) [52]. In the Australian setting, Chao *et al*. reported a statistically significant reduction in acute ≥ grade 1 GI toxicity in HS patients treated with HDR-BT and EBRT compared to non-HS group [33]. Low rates of late grade 1 GI toxicity in both groups were reported (0% in HS group and 7.7% in non-HS group, $p = 0.11$). A systematic review and meta-analysis by Miller *et al*., who included patients treated with BT, EBRT, or combination therapy, showed that reduced rectal dosimetry in HS-treated group translated to a significant reduction in late grade 2 or above GI toxicities as well as significant improvement in bowel-related quality of life at late follow-up [32]. Another systematic review by Ardekani *et al*. focused on patients treated with LDR-BT or HDR-BT also demonstrated a reduction in acute and late GI toxicities post-HS insertion [25]. Furthermore, several other research have also reported significant reduction in acute and late rectal toxicities post-RS insertion in LDR-BT as monotherapy, or as combination therapy [13, 45, 46, 53] in HDR-BT [25, 32, 35, 37, 54, 55], and particularly in the settings of IMRT in large-scale multi-institutional randomized clinical trial [39-41].

Statistical analyses presented in Tables 4 and 5 further support a strong correlation between the reduction of rectal dosimetry (RV_{100}, rectal D_{1cc} and D_{2cc}) and the reduction in acute or late GI toxicities. Significantly, reducing RV_{100} to ≤ 0.5 yielded a lowered rate of late GI toxicity, when compared to the cohort of patients who received RV_{100} > 0.5. This was consistent with findings from Veccia *et al*. who reported improvements in acute and late rectal functions when post-implant RV_{100} was restricted to ≤ 0.5 [7]. Similarly, Shiraishi *et al*. also reported a reduction in rates of grade 2 rectal bleeding in patients treated with ^{125}I BT combined with EBRT, when RV_{100} was ≤ 0.5 ml [30]. Furthermore, reduction of rectal D_{1cc} and D_{2cc} (below ROC values) also demonstrated a significant reduction in acute and late GI toxicities. Adjusting for these confounding effects through multi-variable analysis maintained the reduced acute and late GI toxicity rates for patients with RS insertion, further supporting evidence from the current literature [4-6, 22, 27].

Therefore, the reported reduction in acute and late GI toxicities following RS insertion in this study reaffirms the results of current literature and strengthens understanding in the setting of ^{125}I LDR-BT monotherapy.

Study strength and limitations

The patients' demographics and underlying pathological features of diseases for the two investigated cohorts in this study were comparable in nature, except for cT stage, where a higher proportion of T2a patients were present in the non-RS cohort. However, there was no indication that cT stage was associated with a higher likelihood of GI toxicity, which minimized the probability of difference in cT stage as a strong confounding variable impacting on identified statistically significant difference in acute and late GI toxicities.

One significant advantage of this study was its' demonstration of association between reduced rectal dosimetry and acute and late GI toxicities. Furthermore, the statistical analyses allowed for an assessment of association between the effect of RS on GI toxicity outcomes, adjusting for rectal dosimetry values. This provided a new insight into the efficacy of RS in LDR-BT, which currently lacks sufficient evidence. Although, one limitation of this study was its' relatively small sample size, reducing the power of the study, and inability to detect statistically significant associations between RS and GI toxicities after adjusting for post-rectal D_{1cc} and D_{2cc} values, despite the positive effect of RS on reducing late GI toxicity, as shown by the magnitude of odds ratios from multi-variable analysis.

This multi-institutional approach used in this study, involving multiple community-based private radiation oncology centers, provided a larger sample size with a diverse, yet comparable patients' population, which allowed the data to be easily interpreted and applied by a wider variety of medical practitioners in their clinical practice. It also minimized issues of bias surrounding clinical practice, accessed barriers, and selection bias in single-institutional studies. Significantly, clinical practice, involving patient workup, imaging choice, and treatment modality, remained consistent across different campuses involved in this community-based study.

Despite efforts to minimize selection bias, the risk of bias still exists in this study due to the nature of its' design, which could be further minimized with a randomized clinical trial. The discretion of spacer implantation and choice of RS by the treating urologist was another major limitation of this study, which could be minimized with a blinded study with a 1 : 1 case-control randomization.

The RS cohort had a shorter median follow-up duration when compared to the control cohort, which could contribute to the observed reduction in late GI toxicity outcomes. As such, a study with a longer duration of follow-up could further establish the effect of RS on late GI toxicity.

Conclusions

This Australian community-based retrospective study demonstrated that RS insertion with either HS or HA gel for treatment of low-risk and intermediate-risk PCa patients using ^{125}I LDR-BT was safe and effective in reducing rectal dosimetry as well as decreasing early GI toxicity. Our early data suggests that reduction in rectal dosimetry may translate to lower long-term GI toxicity. This approach also maintained comparable prostate dosimetry and similar rates of acute and late GU toxicities, when compared to patients not treated with a RS insertion. A randomized clinical trial could help further appreciate and quantify the risks and benefits of RS insertion in this clinical setting.

Disclosure

We declare one potential conflict of interest: the corresponding author Associate Professor Michael Chao is an advisory board member for Palette Life Sciences Pty Ltd.

The authors report no conflict of interest.

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