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ORIGINAL ARTICLE

Pudendal nerve injury impairs anorectal function and health related quality of life measures ≥2 years after 3D conformal radiotherapy for prostate cancer

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ABSTRACT

Purpose: To compare GI symptoms, measures of generic and disease specific health related quality of life (HRQoL), anorectal and pudendal nerve function and anal sphincter morphology between (i) patients ≥2 years after 3D conformal radiotherapy (3D-CRT)±high dose rate (HDR) brachytherapy for carcinoma of the prostate and aged matched patients before radiotherapy and (ii) symptomatic and asymptomatic patients ≥2 years after 3D-CRT ± HDR brachytherapy.

Material and methods: Methodology included: (i) modified LENT-SOMA scales for GI symptoms, (ii) EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires for generic and disease specific HRQoL, (iii) anorectal manometry and terminal motor latency for anorectal and pudendal nerve function and (iv) endorectal ultrasound for anal sphincter morphology. GI symptoms, parameters of HRQoL, anorectal and pudendal nerve function and anal sphincter morphology were compared using Mann–Whitney's *U*, unpaired *t* and χ^2 tests.

Results: Impairment of HRQoL bowel symptoms in the patients ≥2 years after 3D-CRT ± HDR brachytherapy was associated with worse anorectal motor and sensory function, internal and external anal sphincter morphology and 5× greater prevalence of pudendal nerve dysfunction compared with age matched patients before radiotherapy. Symptomatic patients had worse (i) HRQoL measures including global quality of life and bowel and urinary symptom scores, (ii) rectal bleeding, fecal urgency and incontinence scores and (iii) a 2× higher prevalence of pudendal nerve dysfunction compared with asymptomatic patients.

Rectal and anal (i) *V* 40 Gy >65%, (ii) Dmax >60 Gy, (iii) pudendal nerve Dmax >60 Gy and (iv) Anal *V* 60 Gy >40% were associated with a greater prevalence of pudendal nerve dysfunction.

Conclusions: 3D-CRT ± HDR brachytherapy for prostate carcinoma, impairs late functional measures including HRQoL, anorectal and pudendal nerve function. Rectal, anal and pudendal nerve radiation dose constraints are proposed for reducing the prevalence of pudendal nerve dysfunction.

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Introduction

External beam radiotherapy (EBRT) is preferred for the curative treatment of localized prostate carcinoma by many, particularly older men [1]. The treatment is associated with a 50% reduction in the 10-year prostate cancer mortality compared with endocrine treatment alone [2]. Despite technological advances, gastrointestinal (GI) symptoms such as increased stool frequency, rectal bleeding, urgency and fecal incontinence (FI) occur in the majority of patients during EBRT. These GI symptoms persist in approximately 50% of patients at 5 years [3–5]. Chronic GI symptoms, particularly rectal urgency and FI result in major impairment of the quality of life of these patients [6]. With the exception of rectal bleeding, the ongoing GI symptoms are often refractory to treatment [6,7]. Furthermore, a prospective, randomized trial of EBRT using 3D conformal radiotherapy (3D-CRT) for prostate cancer reported that soiling and FI occurred in over 50% of patients at 3 years [5], suggesting that the prevalence of anorectal dysfunction even with advanced treatment techniques including IMRT have been under-estimated [3,5].

The pathophysiology of anorectal dysfunction after EBRT for carcinoma of the prostate is not fully characterized. Weakness of the external anal sphincter (EAS) and the internal anal sphincter (IAS), decreased rectal compliance, increased rectal sensitivity and faster distal colonic transit have all been implicated [8–10]. However, it remains uncertain whether the underlying etiology of the radiation-induced anorectal dysfunction is predominantly myogenic or neurogenic in nature.

The pelvic nerves and their branches regulate motor, sensory and autonomic activity in the anorectum. The pudendal nerves innervate the EAS and IAS and are vulnerable to

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Supplemental data for this article can be accessed here.

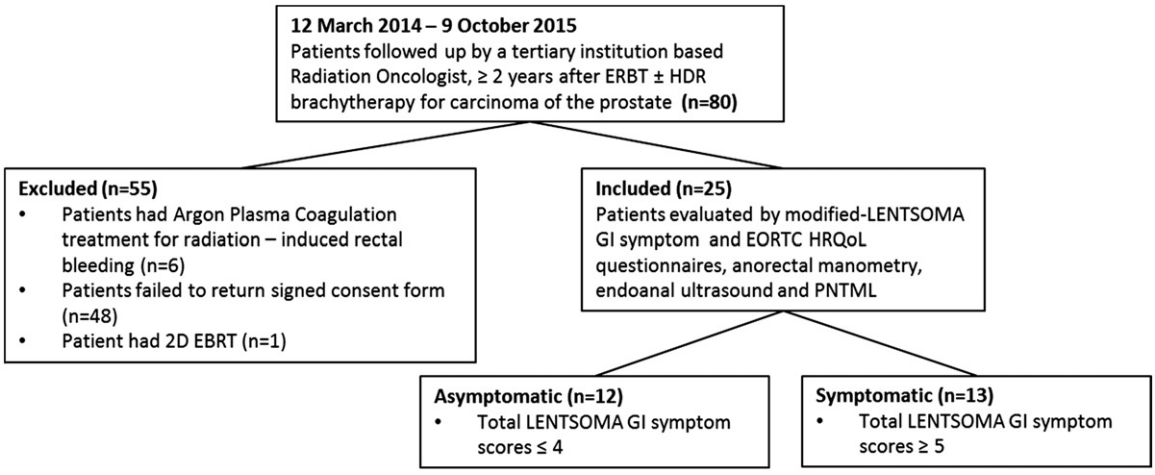

Figure 1. Flow diagram showing patient cohort selected for the study.

damage during radiation treatment of prostate carcinoma. Striated muscle fibers constituting the EAS is considered more resistant to radiation damage compared to neural tissue [8]. There is a paucity of studies examining the role of pudendal nerve injury in radiation-induced anorectal dysfunction.

Our recent data suggest pudendal nerve dysfunction is important in the pathogenesis of FI 3–15 years after EBRT for prostate carcinoma [11]. However, in that study only three of the 17 patients examined were treated with 3D-CRT and radiation dose volume data of organs at risk (OAR) were based on modeling of available CT data only.

The aims of the current study were to further evaluate the etiology of radiation induced anorectal dysfunction by comparing GI symptoms, measures of generic and disease specific health related quality of life (HRQoL), anorectal and pudendal nerve function and anal sphincter morphology between (i) men $\geq$2 years after 3D-CRT ± high dose rate (HDR) brachytherapy and age matched patients before radiotherapy for carcinoma of the prostate and (ii) symptomatic and asymptomatic patients $\geq$2 years after 3D-CRT ± HDR brachytherapy for carcinoma of the prostate.

Material and methods

Study population

The study population was recruited from among 80 patients still attending follow-up during the period between 12 March 2014 and 9 October 2015 after completing EBRT ± HDR brachytherapy $\geq$2 years for localized (UICC T1–T3, N0, M0) prostate carcinoma under the care of a tertiary institution based Radiation Oncologist. Eligibility criteria for the study were (i) completion of 3D-CRT ± HDR $\geq$2 years previously, (ii) no clinical or radiological evidence of relapse, (iii) no therapy likely to influence evaluation of anorectal function such as argon plasma coagulation (APC) therapy for radiation-induced rectal bleeding and/or a constant requirement for anti-diarrheal medication and (iv) signed informed consent to participate in the institutional approved study protocol.

Written information of the study protocol including a consent form previously approved by the institutional research ethics committee was mailed to each patient after being verbally informed of the study protocol in clinic. This was followed by a telephone call two weeks later by one of the graduate scientist research assistants (ADiM). Forty patients declined to participate in the study protocol for the following reasons: (i) feeling unwell from other medical conditions, (ii) not interested, had no time or had concerns about the study protocol (21 including one patient unable to attend because he could not do without loperamide medication for alleged radiation-induced bowel disease) and (iii) transport difficulties [9]. Eight patients who declined the study did not state a reason.

Of the 32 who returned the signed informed consent form, seven patients were excluded due to APC therapy for radiation-induced rectal bleeding ($n = 6$) or radiotherapy with a 2D technique 15 years previously ($n = 1$) (Figure 1).

Of the 25 remaining patients who met all eligibility criteria, 23 received 3D-CRT alone, two had EBRT + HDR brachytherapy (Table 1).

Twelve patients were classified asymptomatic and 13 as symptomatic (Table 1) on the basis of a modified total LENT-SOMA GI symptom score of $\leq$4 and $\geq$5 respectively (4 being the median total modified LENT-SOMA GI symptom score at baseline in one of our previous studies [8]).

Experimental protocol

Each patient underwent the following evaluations: (i) modified Late Effects Normal Tissue – Subjective Objective Management Analytic (LENT-SOMA) GI symptom scales, (ii) generic and disease specific European Organization for Research and Treatment of Cancer (EORTC) HRQoL outcome measures, (iii) anorectal and pudendal nerve function and (iv) anal sphincter morphology.

Modified LENT-SOMA GI symptoms

GI symptoms including stool frequency and consistency, rectal pain, mucous discharge, urgency of defecation and rectal

Table 1. Study population demographics and radiation treatment characteristics for symptomatic and asymptomatic patients.

Patient no.	Age (years)	Body weight (kg)	Body mass index (kg/m^2)	Tumor stage	Treatment	Maximum irradiated prostate volume (cm^3)	Mean radiation dose (Dmean) (Gy)	Maximum radiation dose (Dmax) (Gy)	Time since completion of RT (months)
Symptomatic									
1	78	84	25.5	2	EBRT	198.36	69.89	70.87	83
2	77	108	36.1	1	EBRT	n/a	n/a	n/a	74
3	69	83	25.9	2	EBRT	221.53	73.64	74.77	47
4	83	91	28.2		EBRT	122.78	72.16	73.66	29
5	73	83	30.5	1	EBRT + HDR Brachytherapy	163.83	47.65	48.66	27
6	82	90	27.8	1	EBRT	n/a	n/a	n/a	109
7	77	89	31.5	2	EBRT	n/a	n/a	n/a	81
8	76	66.2	22.4	2	EBRT	252.42	63.93	65.11	41
9	80	79	23.8	3	EBRT	164.59	74.9	76.17	63
10	72	82	30.5	3	EBRT	221.85	70.48	71.29	52
11	82	92	29	3	EBRT + HDR Brachytherapy	233.02	51.82	56.97	26
12	73	100	32.3	2	EBRT	198.62	73.87	75.22	41
13	78	91	28.1	2	EBRT	n/a	n/a	n/a	52
Asymptomatic									
14	83	95	31.3		EBRT	389.78	73.18	74.39	39
15	71	71	24.3	1	EBRT	283.32	70.26	71.86	68
16	71	77	24.9	2	EBRT	208.3	69.44	70.73	61
17	80	85	28.7	2	EBRT	160.14	70.76	71.66	84
18	77	89	27.8	1	EBRT	n/a	n/a	n/a	93
19	76	83	24.8	1	EBRT	236.55	69.26	71.33	83
20	65	93	27.2	3	EBRT	167.56	74.57	75.96	60
21	71	75	26.6	1	EBRT	220.24	70	71.06	70
22	73	82	29.7	1	EBRT	163.85	71.33	69.15	114
23	65	47	17.9	1	EBRT	140.21	69.16	70.66	96
24	80	76	24.8	1	EBRT	n/a	n/a	n/a	156
25	64	99	34.3	1	EBRT	n/a	n/a	n/a	75

bleeding were evaluated using modified LENT-SOMA scales [8]. Each LENT-SOMA GI symptom was scored on a five point (0–4) categorical scale (1–4 corresponding to the four LENT-SOMA grades, 0 in the modified scale representing the absence of the abnormal symptom) [8].

Generic and disease specific HRQoL measures

Validated EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires were used to evaluate generic and disease specific HRQoL, respectively [12,13].

The QLQ-C30 HRQoL questionnaires consist of five functional scales, three general symptom scales, a global health quality of life scale and six single items [12].

The disease specific (prostate cancer) module, QLQ-PR25 HRQoL developed for use with QLQ-C30 HRQoL consists of 25 items in four subscales to evaluate bowel symptoms (four items), urinary symptoms (nine items), sexual function (six items) and hormone treatment-related symptoms (six items) [13].

Anorectal function

Urgency of defecation and FI were evaluated by a four point (0–3) categorical scale questionnaire before measurement of anorectal function [14]. Evaluation of each symptom was based on its frequency and severity. A score of 0 represented <1 episode/week, while a score of 3 represented ≥ 1 episode/day. For severity, 0 denoted absence of the symptom with numerical values up to 3 reflected increasing severity of each symptom [14]. The maximum score for urgency of defecation $= 6$ and FI $= 12$, diurnal and nocturnal FI being scored separately [14].

Anorectal motor function was evaluated with a perfused sleeve and multiport anorectal assembly incorporating a highly compliant polyethylene bag located in the rectum. Anorectal pressures were recorded under resting conditions and in response to squeeze and increased intra-abdominal pressure [8,10].

Anorectal sensory function

The sensation reported by the patient (perception of the stimulus, desire to defecate, or pain) during graded rectal distension of the inflatable polythene bag was recorded [8,10].

Pudendal nerve terminal motor latency (PNTML)

PNTML assessment was performed by an accredited technical officer employing a disposable glove-mounted St Mark's electrode and transrectal nerve stimulation technique (13L40 St Mark's Pudendal Electrode™, Medtronic Functional Diagnostics A/S, Skovlunde, Denmark). Square wave stimuli of 0.05 ms duration and 10 mA were delivered at one-second intervals. The electromyography (EMG) recordings were acquired via a MacLab or PowerLab 8S or 4S system with a MacLab or PowerLab bioamplifier using ScopeTM (V3.4.3-4.1) software (ADInstruments Pty. Ltd, Castle Hill, NSW, Australia). Multiple recordings were taken on each side and the most well defined action potentials selected for the determination of the latency. The mean latency from these multiple curves was determined. Latency was defined as the time between the stimulation of the pudendal nerve at the level of the ischial spine (the electrical pulse being recorded as a stimulus artifact) and commencement of depolarization of the anal sphincter [15]. A lack of pudendal nerve response was defined as no sphincter contraction on EMG recording in response to stimulus [11].

Anal sphincter morphology

Cross sectional images to determine the maximal thickness of both the IAS and EAS were acquired with a 7.5 MHz rotating ultrasonographic scanner (Bruel and Kjaer, Naerum, Denmark) [8,10].

Derivation of radiation dose volume parameters

Radiation dose volume parameters in the study were based on available CT planning scan data files of 18 patients as some of the archived 3D-CRT data files could not be retrieved.

Organs at risk such as the rectum and anal canal were contoured as solid organs, the latter from the anal verge to the anorectal junction just below the pubo-rectalis sling around the posterior wall of the rectum [11]. The pudendal nerve from its entry in the pelvis through the sciatic notch and its exit in the perineum through the ischial spine was also contoured from the CT planning scans [11].

As only two of the total study population of 25 patients had HDR brachytherapy as a supplement to EBRT, the contribution of HDR brachytherapy to the EBRT derived radiation dose volume parameters of the OARs was not included. Furthermore, it is likely that the contribution of HDR brachytherapy to the EBRT derived dose volume parameters of the OARs in this study is likely to be less than that previously reported [16] because unlike the previous report, the supplementary HDR brachytherapy in both patients in this study was delivered with the transrectal ultrasound probe inserted in the rectum.

Data analysis

Modified LENT-SOMA GI symptoms

The medians of the individual and total GI symptom scores in the whole patient group and the symptomatic and asymptomatic patient sub-groups were calculated.

Generic and disease specific HRQoL measures

For the whole patient group and the patient sub-groups, the median scores of QLQ-C30 scales were derived after transforming the means of the raw scores in individual patients to lie between 0 and 100 [12,17]. For the five functioning scales and one global QoL scale, a higher score denotes a better

level of functioning while higher scores in the general symptom and single item scales represent increasing detrimental effects.

The median scores for the four symptom sub-scales of the QLQ-PR25 for the whole patient group and symptomatic and asymptomatic patient sub-groups were derived after transforming the means of the raw scores in individual patients to lie between 0 and 100 [13,17]. As for the QLQ-C30 general symptom and single item scales, higher scores for the four symptom sub-scales of the QLQ-PR25 represent increasing detrimental effects.

Anorectal function

Scores of urgency of defecation and FI were derived for each patient [14]. Semi-automated analysis of the sleeve sensor data determined (i) minimum basal anal pressures and responses to (ii) anal squeeze and (iii) increased intra-abdominal pressure [8,10,14].

The volumes of rectal distension associated with sensory perception and desire to defecate were recorded [8,10,14].

Rectal compliance, based on the maximal slope between 40 and 100 mL of the pressure volume relationship for rectal balloon distension were calculated [8,10,14].

Pudendal nerve terminal motor latency

The percentage of patients who had absent or delayed (>2.6 ms [18]) pudendal nerve response unilaterally and/or bilaterally was calculated.

Anal sphincter morphology

The maximal and mean thickness of both the IAS and EAS were calculated from the endoanal measurements around the anal canal [8,10,14].

Radiation dose volume data

The median and range of the minimum (Dmin), the maximum (Dmax) and the mean (Dmean) doses of the rectum, anal canal and pudendal nerve and the % of each OAR receiving ≥40% (*V* 40 Gy) and ≥60% (*V* 60 Gy) of the prescribed EBRT doses to the prostate were derived from available CT planning data of 18 patients [11].

Statistical analysis

The modified LENT-SOMA GI symptom, the generic and disease specific HRQoL, anorectal function and anal sphincteric morphology data were compared between the whole patient group and the data of age matched patients before 3D-CRT for localized prostate carcinoma [19] using the Mann–Whitney *U* and unpaired *t* tests. Mann–Whitney's *U* test and the unpaired *t* tests were also used to compare the data between the symptomatic versus asymptomatic sub-groups.

Linear regression was used to analyze the relationships among the modified LENT-SOMA GI symptom and anorectal function and anal morphology parameters in the whole patient group.

χ^2 test was used to examine differences between the symptomatic and asymptomatic patients in (i) radiation dose volume parameters and (ii) percentages of patients with absent or delayed pudendal nerve responses unilaterally and/or bilaterally.

A p value of ≤.05 was considered statistically significant in all analyses.

Results

Demographics

The median age (range) of the 25 patients was 77 (64–83) years and median (range) time since completion of EBRT ± HDR brachytherapy was 63 (26–156) months. The median (range) maximum irradiated volume which included the prostate as its target was 203.5 (122.8–389.8) cm^3. The median (range) of mean (Dmean) and maximum (Dmax) EBRT doses to the planning target volume (PTV) of the prostate were 70.1 (47.7–74.9) Gy and 71.3 (48.7–76.2) Gy, respectively (Table 1).

Comparison between patient groups

There were no differences including age [median (range) = 73 (57–84) years], body weight and body mass index between the age matched and patients in this study.

Comparison between patient sub-groups

There were also no differences between the ages of the symptomatic [median (range) = 77 (69–83) years] versus asymptomatic [median (range) = 75 (64–83) years] patients in this study. The two patients who received HDR brachytherapy supplementary to EBRT were classified as symptomatic and symptomatic patients had completed radiotherapy significantly earlier [median (range) = 52 (25–108) months] than asymptomatic patients [83 (39–156) months], $p < .05$ (Table 1). The median (range) of irradiated prostate volume 198.6 (122.8–252.4), Dmean 70.5 (47.6–74.9) Gy and of Dmax 71.3 (48.7–76.2) Gy were no different in symptomatic (EBRT component only) from the corresponding data of 208.3 (140.2–389.8) mL, 70.3 (69.2–74.6) Gy and 71.3 (69.2–76.0) Gy in asymptomatic patients (Table 1).

Modified LENT-SOMA GI symptoms

Comparison between patient groups

Patients in this study had significantly higher modified LENT-SOMA frequency and urgency of defecation, rectal bleeding and mucous discharge scores relative to the data in age matched patients before radiotherapy (Supplementary Table).

Table 2. Comparison of modified LENT-SOMA GI symptoms and EORTC generic (QOL-C30) and disease specific (QLQ-PR25) HRQoL data between symptomatic and asymptomatic patients.

LENT-SOMA	Symptomatic patients	Asymptomatic patients	*p* Value
Frequency	1 (0–3)	1 (0–1)	ns
Diarrhea	1 (0–2)	0 (0–2)	ns
Pain	0 (0–2)	0 (0–2)	ns
Mucous	1 (0–3)	0 (0–1)	ns
Urgency	3 (1–4)	1 (0–4)	<.01
Bleeding	1 (0–3)	0 (0–1)	<.001
EORTC QLQ-C30			
Physical functioning	87 (60–100)	100 (73–100)	ns
Role functioning	100 (50–100)	100 (67–100)	ns
Emotional functioning	75 (58–100)	96 (67–100)	=.05
Cognitive functioning	83 (50–100)	83 (67–100)	ns
Social functioning	83 (50–100)	100 (67–100)	<.001
Global health status	67 (50–83)	83 (17–100)	<.05
Dyspnea	0 (0–33)	0 (0–33)	ns
Insomnia	33 (0–100)	33 (0–33)	ns
Appetite loss	0 (0–33)	0 (0–0)	ns
Nausea and vomiting	0 (0–17)	0 (0–17)	ns
Constipation	33 (0–67)	33 (0–33)	ns
Diarrhea	0 (0–100)	0 (0–33)	=.05
Fatigue	33 (0–44)	11 (0–33)	<.05
Pain	0 (0–33)	0 (0–100)	ns
Financial difficulty	0 (0–33)	0 (0–0)	ns
EORTC QLQ-PR25			
Urinary symptoms	25 (0–58)	10 (0–25)	<.05
Bowel symptoms	25 (8–42)	0 (0–25)	<.001
Hormonal treatment-related symptoms	11 (0–50)	6 (0–33)	ns

Table 3. Comparison of anorectal function and anal sphincter morphology data between whole patient group and age matched patients before radiotherapy.

ARM	Whole patient group	Age matched patient group	*p* Value
Basal pressure (mmHg)	46 ± 4	63 ± 3	<.01
Squeeze pressure (mmHg)	105 ± 8	154 ± 8	<.0001
↑Intra-abdominal pressure (mmHg)	82 ± 5	106 ± 5	<.01
IAS (mm)	2.1 ± 0.1	2.6 ± 0.1	<.05
EAS (mm)	8.0 ± 0.3	9.3 ± 0.3	<.01
Threshold perception (mL)	14 ± 1	16 ± 2	ns
Desire to defecate sensation (mL)	68 ± 8	97 ± 9	<.05
Rectal compliance (mL/mmHg)	3.3 ± 0.3	5.1 ± 0.4	<.01
FI score	2 (0–8)	0 (0–1)	<.001
Urgency score	2 (0–6)	0 (0–3)	<.001
Number of bowel actions/week	10.5 (7–24.5)	7 (3.5–21)	<.05

Comparison between patient sub-groups

Symptomatic patients had significantly higher modified LENT-SOMA urgency of defecation and rectal bleeding scores compared with asymptomatic patients (Table 2).

Generic and disease specific EORTC HRQoL measures

Comparison between patient groups

Except for lower cognitive functioning scores in the whole patient group, there were no significant differences in the EORTC QLQ-C30 measures in the comparisons with the age matched patients (Supplementary Table). Patients in this study also had worse (higher) bowel symptom scores for the EORTC QLQ-PR25 instrument compared with the data of age matched patients (Supplementary Table).

Comparison between patient sub-groups

Emotional and social functioning scales, diarrhea and fatigue scores as well as global health quality of life measured by the QLQ-C30 instrument were worse in the symptomatic versus the asymptomatic patients (Table 2). Urinary and bowel function scores measured by the QLQ-PR25 questionnaires were also worse (higher) for the symptomatic patients (Table 2).

Anorectal function

Comparison between patient groups

All parameters of anorectal motor and sensory function except for threshold volumes for sensory perception were significantly worse in the patients in this study compared to baseline data of the aged matched group (Table 3).

Comparison between patient sub-groups

Fecal incontinence scores were worse in the symptomatic compared to the asymptomatic patients (Table 4).

Table 4. Comparison of anorectal function and anal sphincter morphology data between symptomatic and asymptomatic patients.

ARM	Symptomatic Patients	Asymptomatic Patients	*p* Value
Basal pressure (mmHg)	42 ± 5	51 ± 6	ns
Squeeze pressure (mmHg)	92 ± 9	119 ± 11	ns
↑Intra-abdominal pressure (mmHg)	78 ± 7	86 ± 8	ns
IAS (mm)	2.3 ± 0.2	2.1 ± 0.2	ns
EAS (mm)	8.4 ± 0.4	7.6 ± 0.3	ns
Threshold perception (mL)	15 ± 2	13 ± 1	ns
Desire to defecate sensation (mL)	55 ± 8	81 ± 14	ns
Rectal compliance (mL/mmHg)	3.4 ± 0.4	3.2 ± 0.4	ns
FI score	3 (0–8)	0 (0–3)	<.01
Urgency score	3 (0–6)	0 (0–5)	ns
Number of bowel actions/week	14 (7–24.5)	10.5 (7–17.5)	ns

Pudendal nerve terminal motor latency

Comparison between patient groups

Unilateral and/or bilateral pudendal nerve responses were delayed in 13/24 (54%) of the patients in this study compared to only 2/20 (10%) patients in the aged matched patient group ($p < .0001$, data not shown).

Comparison between patient sub-groups

Unilateral and/or bilateral pudendal nerve responses were delayed in 9/13 (69%) of symptomatic compared to only 4/11 (36%) of asymptomatic patients ($p < .0001$, data not shown).

Anal sphincter morphology

Comparison between patient groups

The thickness of both IAS and EAS was less in the patients in this study compared with that of the age matched patients (Table 3).

Comparison between patient sub-groups

However, there was no difference in IAS and EAS thickness between symptomatic and asymptomatic patients (Table 4).

Linear regression analysis

In the whole patient group, modified LENT-SOMA urgency of defecation and mucous discharge scores were both inversely related to basal anal pressures ($r = -0.40$, $p < .05$ and $r = -0.39$, $p < .05$ respectively, data not shown).

There were also inverse relationships between LENT-SOMA urgency of defecation scores and anal pressures in response to increased intra-abdominal pressure ($r = -0.48$, $p < .05$, data not shown) and between LENT-SOMA mucous discharge scores and anal squeeze pressures ($r = -0.52$, $p < .01$, data not shown).

In addition, FI scores in the anorectal function symptom questionnaire (which was directly related to LENT-SOMA mucous discharge scores [$r = 0.60$, $p < .01$], data not shown) was inversely related to basal anal ($r = -0.39$, $p = .05$, data not shown) and squeeze ($r = -0.39$, $p = .05$, data not shown) pressures.

Table 5. Median (range) of baseline (planning) dose volume histogram parameters of outer rectal wall, anal wall and pudendal nerve.

Whole group	Outer rectal wall	Anal wall	Pudendal nerve
Volume (cm^3)	59 (28.8–242.4)	33.1 (18.3–52.3)	3.6 (2–5.4)
Dmean (Gy)	49.6 (30.7–63.8)	35.4 (15.8–58.5)	53.1 (25.5–67.3)
Dmax (Gy)	70.9 (48.6–75.3)	69.9 (47.6–75.1)	70.2 (48.2–74.2)
$V \geq 40$ Gy (%)	74.2 (28.1–100)	36.2 (6.7–85.3)	82 (17.1–100)
$V \geq 60$ Gy (%)	50.5 (14.9–72)	17.78 (0–58.5)	35.5 (0–85)

Radiation dose volume parameters

Radiation dose volume data of OARs for the whole patient group in this study are shown in Table 5.

Comparisons of the data between symptomatic and asymptomatic patients revealed no significant differences.

The prevalence of delayed unilateral and/or bilateral pudendal nerve conduction was higher for (i) rectal and anal V 40 Gy >65% versus rectal and anal V 40 Gy <65% ($p < .0001$ for both, data not shown), (ii) rectal and anal Dmax >60 Gy versus Dmax < 60 Gy ($p < .0001$ for both, data not shown), (iii) pudendal nerve Dmax >60 Gy versus Dmax < 60 Gy ($p < .0001$, data not shown) and (iv) Anal V 60 Gy >40% versus anal V 60 Gy < 40% ($p < .001$, data not shown).

Discussion

The study data show that, ≥2 years after 3D-CRT ± HDR brachytherapy for carcinoma of the prostate, patients had (i) impairment of HRQoL bowel symptoms, (ii) worse anorectal motor and sensory function, (iii) thinner internal and EASs and (iv) ~5× greater prevalence of pudendal nerve dysfunction compared to age matched patients before radiotherapy. Furthermore, symptomatic patients had (i) impairment of several generic HRQoL functioning, diarrhea and fatigue measures leading to a reduction in global quality of life scores in addition to worse HRQoL bowel and urinary symptom scores, (ii) worse rectal bleeding, urgency and FI scores and (iii) ~2× higher prevalence of pudendal nerve dysfunction compared to asymptomatic patients after radiotherapy.

The association of impairment of HRQoL bowel symptoms with worse anorectal motor function ≥2 years following 3D-CRT ± HDR brachytherapy in the whole patient group in this study supports previous reports that late anorectal dysfunction rather than rectal bleeding has a greater and more persistent adverse impact on patient reported outcomes [6,8,12]. That symptomatic patients had impairment of a number of

generic HRQoL measures including global quality of life and worse bowel symptom scores compared with asymptomatic patients is consistent with a previous report that worse global quality of life was associated with increased FI scores levels after radiotherapy for carcinoma of the prostate [12].

However, the major new observation in the current study of 5× higher prevalence of pudendal nerve dysfunction ≥2 years after 3D-CRT ± HDR brachytherapy compared with age matched patients before radiotherapy has important implications for optimizing current radiotherapy treatment planning and delivery techniques to reduce its prevalence and consequent impairment of anorectal function and HRQoL. Currently, universally recognized OAR in planning radiotherapy for carcinoma of the prostate is the anorectum (combining anal canal and rectum), small and large bowel (only if the pelvic nodes are the target of irradiation) and the bladder although we and others have suggested that the anal canal and rectum should be contoured separately [3,20]. Individual pelvic floor muscles have also been proposed as 'organs' at risk [21], The findings of a 5× higher prevalence of pudendal nerve dysfunction 2 years or more after EBRT ± HDR brachytherapy compared with age matched patients before radiotherapy is consistent with the findings of our previous study [11] although no absent pudendal nerve responses were observed in the present study. The lesser impairment of pudendal nerve function in this study is reflected in the absence of evidence of atrophy of the anal sphincters on ultrasound although the internal and EASs were thinner in the patients ≥2 years after 3D-CRT ± HDR brachytherapy compared with age matched patients before radiotherapy. The differences in % of patients treated with 3D-CRT in this study (100%) compared with our previous study (18%) and in the median time since completion of radiotherapy (5 years for present versus 8 years for previous study) suggest that greater sparing by the universal application of 3D-CRT in this study and/or progressive damage to the pudendal nerves in the previous study [20] are likely explanations for the less severe pudendal nerve dysfunction reported here.

The prevalence of unilateral and/or bilateral pudendal nerve injury in the current study was increased if a number of actual (rather than modeled in our previous study [11]) radiation dose volume parameters were exceeded including pudendal nerve, rectal and anal Dmax >60 Gy. Although these parameters have not been previously reported as dose constraints for radiotherapy treatment planning, Dmean anal and *V* 40 Gy anal have been associated respectively with an increased risk of FI and increased total GI symptom scores after radiotherapy for prostate carcinoma [20,22]. Differences in the definition of the anal canal (contoured separately from the rectum) and statistical analyses of the data between the studies were proposed to account for the finding of a volume [20] as opposed to a dose [22] constraint in the previous studies [20,22]. It is interesting to note that the current study which used the same contouring definitions of rectum and anal canal as one of our previous studies [20] had similar dose volume parameters of the contoured OAR's and *V* 40 Gy anal ≥65% was also found to be associated with an increased prevalence of GI OAR damage after radiotherapy.

The data in this study provide further support for separate contouring of the rectum and anal canal in radiotherapy treatment planning for prostate carcinoma and also suggest that the pudendal nerve should be considered as an 'organ' at risk of radiation damage. We propose that the maximum dose to each contoured pudendal nerve should not exceed 60 Gy and the *V* 40 Gy for rectum and anal canal should be kept below 65%. These dose constraints should not be difficult to meet with more sophisticated techniques of radiation dose delivery involving intensity modulation of the radiation treatment (IMRT) beams and could reduce the continuing high (up to 65%) rates of chronic anorectal toxicity reported for IMRT of carcinoma of the prostate [3].

There are several potential weaknesses in this study. These include the study of a relatively small sample of patients retrospectively which hampers meaningful subgroup analyses based on the five previously described late radiation-induced bowel syndromes [23] and the derivation of the radiation dose volume parameters of the OARs based on a single planning CT scan of the pelvis previously reported to be problematic in the proper understanding of dose volume relationships of OARs at risk of late GI toxicity [24]. However, we believe that these are outweighed by the strengths which include (i) a standard treatment technique of the patients and follow-up protocol by a single tertiary institution based radiation oncologist, (ii) comparisons of the data with a population of age matched patients before radiotherapy for carcinoma of the prostate although comparisons with the baseline data of the same patient group would have been preferable and (iii) meaningful significant relationships between the modified LENT-SOMA urgency of defecation, mucous discharge scores and anorectal motor function parameters which not only confirms previous reports that weakness of the IAS and EAS contribute to anorectal dysfunction [7,8,14] but also suggests that the underlying etiology of the weakness is neurogenic. Nevertheless, the long time delay between development of symptoms and investigation in this and our previous study [11] suggest the need for well designed prospective studies with prolonged follow up to confirm the findings reported in this study.

Disclosure statement

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