Chapter

Pathophysiology, Natural History and Approaches to Treatment and Prevention of Radiation Proctitis

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Abstract

Chronic radiation proctitis (CRP), characterized by increased frequency and urgency of defecation, fecal incontinence and rectal bleeding, is an under-estimated cause of morbidity after pelvic irradiation for urological and gynecological malignant diseases. Despite improvements in radiotherapy technology, 90% of patients have persistent long term symptoms and 50% of all patients report impairment of quality of life after pelvic radiotherapy. Research by an Australian group of clinician scientists, including prospective, longitudinal and retrospective studies as well as a randomized trial of two current approaches used for the treatment of haemorrhagic radiation proctitis over a time span exceeding two decades, have provided important insights into the prevalence, pathophysiology natural history and treatment of CRP. The findings have important implications for the management and amelioration if not prevention of CRP. Data from 4 selected studies conducted by the Australian group, each characterizing changes in anorectal function and anal sphincteric morphology, are first presented. This is followed by discussion of how the findings have led to the development of more rational therapeutic interventions for CRP and how novel approaches designed to reduce the prevalence of CRP when combined could lead to its elimination in the foreseeable future.

Keywords: Pelvic cancer, radiotherapy, anorectal physiology, haemorrhagic proctitis, quality of life

1. Introduction

Among the estimated 300,000 patients per year worldwide undergoing radiotherapy for pelvic malignant diseases such as carcinoma of the uterine cervix and corpus, bladder and prostate, nine out of 10 will develop a permanent change in their bowel habit [1]. Furthermore, this UK group and an Australian group of clinician scientists have independently reported that 50% of all patients report an adverse impact on activities of daily living (ADL) after pelvic radiotherapy [1, 2].

The radiation induced bowel symptoms which have the greatest adverse effect on ADL are anorectal symptoms such as increased frequency and urgency of defecation, fecal incontinence and rectal bleeding collectively referred to as Chronic Radiation Proctitis (CRP) [1–3].

The prevalence of CRP is uncertain. Studies using physician based questionnaires such as the Radiation Therapy Oncology Group (RTOG) scales report a prevalence of only 5–10% [4]. However, because these scales do not evaluate common anorectal symptoms such as urgency of defecation and fecal incontinence, physician based scales probably under-estimate the prevalence of CRP. In support of this, studies that have included patient-based questionnaires such as the Late Effect Normal Tissue – Subjective Objective Management Analytic (LENT – SOMA) scales have reported that up to 78% of patients have persistent anorectal symptoms after radiotherapy for prostate carcinoma [5–9]. Although persistent anorectal symptoms impair the daily activities of 50% of all patients 5 years after pelvic radiotherapy, the pathophysiology of anorectal dysfunction has not been fully characterized and its treatment is unsatisfactory. Previous physiological studies in patients with anorectal dysfunction after radiotherapy have been limited either by methodological inadequacies [10] or lack of follow-up studies beyond 2 years [11, 12].

The rationale for the selection of each of the 4 listed studies for discussion in this chapter are provided under the sub-headings below:

1. Pathophysiology and natural history of anorectal sequelae following radiation therapy for carcinoma of the prostate [2]

   In view of the limitations of previous physiological studies of anorectal function after radiotherapy for prostate carcinoma, 5 year data from an Australian prospective, longitudinal study of a subset of patients who participated in a Phase III randomized trial comparing a 4 week course of (hypofractionated) radiotherapy with the then conventional 6.5 week schedule of radiotherapy for carcinoma of the prostate [13] will first be presented.

2. A retrospective study of the effects of pelvic irradiation for gynecological cancer on anorectal function [14])

   As at least a third of patients, who have had pelvic radiotherapy for gynecological cancer are reported to suffer significant radiation bowel sequelae [1], anorectal function data from the above retrospective study will be presented next.

3. Argon Plasma Coagulation Therapy versus Topical Formalin for intractable rectal bleeding and anorectal dysfunction after radiation therapy for prostate carcinoma [15]

   As rectal bleeding is the second most common reason for referral to a gastroenterologist after pelvic radiotherapy even though it impairs the ADL's of only 6% of patients [1], data from the only randomized trial of two current approaches used in the treatment of haemorrhagic radiation proctitis above will follow.

4. Pudendal nerve injury impairs anorectal function and health related quality of life measures ≥2 years after 3D conformal radiotherapy for prostate cancer [16]

   Previous studies of the pathophysiology of anorectal dysfunction after radiotherapy for carcinoma of the prostate including our own have implicated weakness of the external anal sphincter (EAS) and internal anal sphincter (IAS), decreased rectal compliance, increased rectal sensitivity and faster distal colonic transit [2, 17, 18]. The underlying pathogenesis proposed for the

observed changes in anorectal dysmotility is either myogenic or neurogenic. However, as muscle tissue particularly striated muscle constituting the EAS is more resistant to radiation damage than neural tissue [2], evidence of pudendal nerve injury after radiotherapy for prostate cancer is presented in the above study [16]. In addition, the editorial accompanying the publication states that the findings show the way forward for the restoration of bowel health of patients who have been adversely affected following pelvic radiotherapy for urological and gynecological malignant diseases [19].

2. Eligibility criteria, experimental protocol, data presentation and interpretation of the studies selected for presentation in this chapter

2.1 Pathophysiology and natural history of anorectal sequelae following radiation therapy for carcinoma of the prostate [2]

2.1.1 Subject selection criteria

The 34 patients, median age = 68 (range 54–79) years, selected for the above study met the following eligibility criteria:

i. Were part of the 217 total patient population participating in a previous Phase III randomized trial of two radiation dose schedules [13]

ii. Have completed (7) serial evaluations (before radiotherapy, at 1 month and at 1 yearly intervals to 5 years after completion of radiotherapy) of anorectal function using the same manometric assembly

iii. Have not needed treatment intervention likely to influence anorectal function such as a constant requirement for antidiarrhoeal medication and argon plasma coagulation therapy (APC) for rectal bleeding

iv. Have provided signed informed consent

Of the total patient population of 217 patients, 86 patients (57 completed two serial evaluations of anorectal function using an earlier manometric assembly which meant that later serial measurements were no longer comparable, 5 started radiotherapy before baseline evaluation and 24 patients died before 5 years), failed to meet eligibility criterion (ii), 12 patients, who required APC for rectal bleeding after radiotherapy, failed eligibility criterion (iii) and 85 patients, who withdrew consent for anorectal manometry after radiotherapy because of distant domicile from the laboratory, failed eligibility criterion (iv).

2.1.2 Experimental protocol

Each of the 34 patients meeting all eligibility criteria for the study underwent evaluations of (i) gastrointestinal symptoms (modified LENT-SOMA scales including effect on activities of daily living (ADL), (ii) anorectal motor and sensory function (manometry with a perfused sleeve and multiport assembly incorporating a highly compliant polyethylene bag in the rectum) and (iii) anal sphincteric morphology (endoanal ultrasound) before radiotherapy and at 1 month, then yearly for 5 years after completion of radiotherapy.

2.1.3 Data presentation and interpretation

Total GI symptom scores increased after radiotherapy and remained above baseline levels at 5 years (**Table 1**). At this time, 48% of patients reported impairment of ADL [2].

The prevalence of persistent urgency of defaecation (44%) was doubled that of rectal bleeding (21%) at 5 years. The % of patients free from the risk of urgency of defecation was significantly less than that of rectal bleeding (**Figure 1**).

All measures of anorectal motor function remained below baseline levels at 5 years (**Table 2**). Furthermore, anal pressures in response to voluntary squeeze and increased intra-abdominal pressure progressively decreased after radiotherapy.

The volume for first perception of rectal distension and that associated with the desire to defaecate both decreased after radiotherapy although only threshold

	Baseline	1 mo	1 y	2 y	3 y	4 y	5 y	ANOVA P value
Stool frequency	0(0–2)	1(0–2)	1(0–2)	1(0–2)	1(0–1)	1(0–2)	1(0–1)	0.05
Stool Consistency	0(0–1)	0(0–2)	0(0–2)	0(0–2)	0(0–2)	0(0–1)	0(0–2)	ns
Rectal Pain	0(0–1)	0(0–3)	0(0–1)	0(0–1)	0(0–1)	0(0–1)	0(0–2)	<.01
Rectal mucous discharge	0(0–2)	0(0–4)	0(0–3)	0(0–3)	0(0–3)	0(0–3)	0(0–3)	<.01
Urgency of defecation	0(0–3)	0(0–4)	1(0–3)	1(0–3)	1(0–4)	1(0–3)	1(0–3)	ns
Rectal bleeding	0(0–2)	0(0–2)	0(0–2)	0(0–3)	0(0–3)	0(0–2)	0(0–4)	ns
Total GI symptom	2(0–4)	3(0–10)	3(0–9)*	3(0-9)*	3(0-7)†	3(0–9)*	3(0-9)*	<.01

Abbreviations: *ANOVA, analysis of variance; GI, gastrointestinal; ns, not significant.*

**P < .05 Compared with baseline.*

†P < .01 Compared with baseline.

From Yeoh et al. [2], with permission.

Table 1.
Median (range) anorectal symptoms at baseline and 1 month, annually to 5 years after radiation therapy for prostate carcinoma.

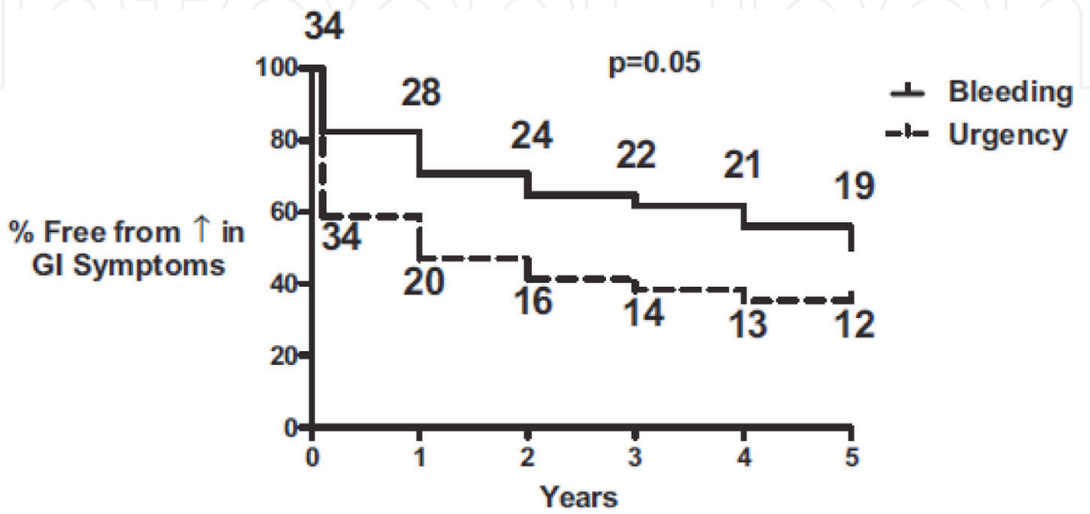

Figure 1.
Percent of patients free from urgency of defaecation vs. rectal bleeding 5 years after radiation therapy. GI = gastrointestinal. (From Yeoh et al. [2], with permission).

	Baseline	1 mo	1 y	2y	3y	4y	5y	ANOVA *P* Value
Basal pressure (mm Hg)	65 ± 3	63 ± 3	59 ± 3	60 ± 3	54 ± 3†	57 ± 3	56 ± 3*	<.001
Squeeze Pressure (mm Hg)	128 ± 10	126 ± 9	106 ± 6*	105 ± 6†	104 ± 5†	103 ± 6†	99 ± 6‡	<.0001
Increased intra-abdominal Pressure (mm Hg)	104 ± 5	99 ± 4	96 ± 5	99 ± 5	94 ± 4	92 ± 5	90 ± 5*	<.05
First Perception (mL)	24 ± 2	17 ± 1†	17 ± 1†	15 ± 1‡	14 ± 1‡	14 ± 1‡	15 ± 1‡	<.0001
Desire to defecate (mL)	63 ± 7	44 ± 5	58 ± 6	40 ± 4*	42 ± 3	51 ± 6	60 ± 8	<.0001
Rectal compliance(mL)	8.2 ± 0.6	7.4 ± 0.5	6.8 ± 0.7	6.2 ± 0.8*	6.4 ± 0.7	5.7 ± 0.5†	5.5 ± 0.6†	<0.001
IAS thickness(mm)	2.4 ± 0.1	2.2 ± 0.1	2.2 ± 0.2	2.1 ± 0.1	2.1 ± 0.1	2.2 ± 01	2.3 ± 0.1	ns
EAS thickness (mm)	10.7 ± 0.5	11.2 ± 0.5	11.2 ± 0.5	10.5 ± 0.5	10.3 ± 0.7	9.6 ± 0.4	9.7 ± 0.7	Ns

Abbreviations: *ANOVA, analysis of variance; EAS, external and sphincter; IAS, internal anal sphincter; ns, not significant; SE, Standard error.*

**P < .05 compared with baseline.*

†P < .01 compared with baseline.

‡P < .0001 compared with baseline.

From Yeoh et al. [2], with permission.

Table 2.

Mean (± SE) anal pressurres (sleeve), rectal sensory volumes, rectal compliance, and anal sphincter thickness at baseline and I month, annually to 5 years after radiation therapy for prostate carcinoma.

volumes for sensory perception at 5 years remained below those recorded at baseline (**Table 2**). Rectal compliance progressively reduced with time after radiotherapy and remained persistently lower at 5 years compared with that recorded at baseline **Table 2**).

Radiotherapy had no effect on the thicknesses of the IAS and EAS (**Table 2**).

There were no differences in any of the GI symptoms nor in any anorectal functional and anal sphincteric morphological measurements between patients randomized to the 2 radiation dose schedules.

5 years after radiotherapy for carcinoma of the prostate, persistent GI symptoms continue to have a significant impact on ADL of almost 50% of all patients. At this time, the prevalence of urgency of defecation (44%) was doubled that of rectal bleeding (21%). Increased GI symptoms after radiotherapy were associated with progressive or persistent reductions of basal anal pressures and pressures in response to voluntary squeeze and increased intra-abdominal pressures, rectal compliance and volumes of sensory perception and desire to defaecate. These physiological changes, which suggest weakness of the IAS and EAS as well as stiffness of the rectal wall and consequent increased rectal sensitivity, are the pathogenetic basis for anorectal dysfunction after radiotherapy for carcinoma of the prostate. The etiology of the motility changes is likely to be neurogenic in the intrinsic neural network in the bowel wall and/or extrinsic nerve supply such as the pudendal nerves since muscle tissue, particularly striated muscle is more resistant to radiation damage.

2.2 A retrospective study of the effects of pelvic irradiation for gynecological cancer on anorectal function [14]

2.2.1 Subject selection criteria

The 15 patients, median age = 67 (range 47–84) years, selected for the study met the following eligibility criteria:

i. Were part of the 33 total patient population who completed pelvic and abdominal irradiation 5–10 years earlier for carcinoma of the cervix (n = 30) and endometrium (n = 3) who participated in a previous prospective longitudinal study of changes in gastrointestinal function after pelvic radiotherapy [20]

ii. Had not needed treatment intervention likely to influence anorectal function such as a constant requirement for antidiarrhoeal medication

iii. Had provided signed informed consent

Of the original total patient population of 33 patients, 6 had died and 2 had been lost to follow-up since completing the previous study [20]. The 25 remaining patients were invited to participate in this study, 10 refused including two patients who had intermittent episodes of rectal bleeding.

9 healthy females, median age = 63 (range 41–70) years served as control subjects.

2.2.2 Experimental protocol

The following parameters were assessed in each subject: (i) anorectal symptoms (questionnaire), (ii) anorectal motor and sensory function (manometry with a perfused sleeve and multiport assembly incorporating a highly compliant latex

balloon in the rectum and concurrent electromyography of the anal sphincters) and (iii) anal sphincteric morphology (endoanal ultrasound).

2.2.3 Data presentation and interpretation

Total anorectal symptom scores was significantly greater in the patients compared with the control subjects (**Table 3**). Urgency of defaecation was the most frequent symptom, occurring in 10 of the 15 patients (67%). Four of these patients also had fecal incontinence [14]. Urgency of defecation in eight of the 10 patients resulted in changes in lifestyle such that the patients were either housebound or could only go out if there was a toilet nearby [14].

Basal minimum pressures just proximal to the anal canal (4 cm from the anal verge) were lower in the patients than the control subjects ($p = 0.05$) and there was a trend for lower basal maximum pressures at the same site ($p = 0.07$, **Table 4**).

Squeeze pressures measured at the sleeve sensor and at 4 cm from the anal verge were lower in the patients ($p < 0.05$, **Table 4**) and were below the control range in five patients [14].

In the patients, residual anorectal pressures measured at 0.5 cm from the anal verge in response to rectal distension were less ($p \leq 0.05$) at volumes of 10 ml, 20 ml and 40 ml (**Table 5**). There was also a trend for lower pressures in the patients at the highest (100 ml) volume ($p = 0.09$).

A higher proportion of patients perceived the desire to defecate at lower rectal volumes than the controls ($p < 0.05$, **Figure 2**). The slope of the pressure/volume relationship associated with rectal distension volumes of 20 ml, 40 ml, 60 ml, 100 ml and overall slope was greater in the patients ($p < 0.05$, $p < 0.01$, $p < 0.001$, $p < 0.001$ and $p < 0.05$ respectively than the controls, suggesting that rectal compliance was reduced in the patients (**Figure 3**).

There were no differences in external anal sphincteric electrical activity between the patients and control subjects in response to voluntary squeeze and blowing up a party balloon (**Table 4**). Either basal pressures, pressures generated in response to rectal distension, voluntary squeeze and blowing up a party balloon were below the control range in 14 of the 15 patients, including all 10 patients with anorectal symptoms [14].

There was no difference in mean EAS and IAS thickness between the two groups (**Table 4**) nor difference in thicknesses of the EAS and IAS in patients with and without urgency of defaecation [14].

The data indicate that (i) urgency of defaecation, occurring in 10 out 15 (67%) of patients 10–15 years after pelvic irradiation for gynecological cancer resulted in eight of the 10 patients being either housebound or only able to go out if there was a toilet nearby, (ii) anorectal symptoms were associated with multiple parameters of anorectal dysfunction including weakness of the external anal sphincter, stiffness of the rectal wall and consequent increase in rectal sensitivity.

2.3 Argon plasma coagulation therapy versus topical formalin for intractable rectal bleeding and anorectal dysfunction after radiation therapy for prostate carcinoma [15]

2.3.1 Subject selection criteria

The 30 patients, median age = 72 (range 49–87) years selected for the study met the following eligibility criteria:

i. Had completed radiotherapy for prostate carcinoma ≥6 months previously

Parameters/ subjects	Fecal incontinence			Urgency of defecation	Symptom score*	No. of bowel actions/ week*	No. of babies*	No. with large babies	No. who had forceps
	Diurnal	Nocturnal	Both						
Patients	3/15	1/15	10/15	10/15†	3‡(0-8)	13(13-28)	3(0–12)	4/15	3/15
Normal	0/9	0/9	1/9	1/9	0(0)	7(7–14)	3(0–4)	2/9	2/9

Median (range).

†P < 0.01.

‡P < 0.001 *Compared to normals.*

From Yeoh et al. [14], with permission.

Table 3.
Anorectal symptoms including bowel habits and obstetric parameters in patients and normal subjects.

	Normal	Patients	*p*-Value
EAS (mm)	8.8 ± 0.5	9 ± 0.4	0.78
IAS (mm)	2.8 ± 0.2	2.3 ± 0.2	0.65
B_{max} (mmHg)			
Anal 0.5 cm†	64 ± 12.5	45.1 ± 5.5	0.13
Sleeve	58.7 ± 6.3	53.3 ± 6.2	0.58
Anorectal 4 cm†	22 ± 5.8	12.1 ± 1.9	0.07
B_{min} (mmHg)			
Anal 0.5 cm†	32.2 ± 8.2	33.1 ± 5.0	0.93
Sleeve	44.3 ± 5.6	41.5 ± 5.9	0.75
Anorectal 4 cm†	14.1 ± 3.3	8.1 ± 1.0	0.05
Voluntary squeeze (mmHg)			
Anal 0.5 cm†	108.2 ± 21.6	70 ± 10.0	0.08
Sleeve	103 ± 10.2	68.1 ± 7.2	0.01
Anorectal 4 cm†	26.4 ± 4.6	16.3 ± 1.8	0.03
Change EMG activity (mm)	6.7 ± 1.8	6.2 ± 0.8	0.75
Blowing up a party balloon			
Anal 0.5 cm†	61.8 ± 11.6	49.4 ± 0.8	0.35
Sleeve	70.1 ± 7.5	65.6 ± 7.8	0.7
Anorectal 4 cm†	35.8 ± 3.7	30.5 ± 2.2	0.21
Change EMG activity (mm)	3.8 ± 1.0	3.4 ± 0.5	0.75

**Data are mean values ±SEM.*

†Manometric port distances from anal verge.
From Yeoh et al. [14], with permission.

Table 4.
Maximum thickness of IAS and EAS and anorectal pressures (basal, in response to voluntary squeeze and blowing up a party balloon).

ii. had intractable rectal bleeding (defined as ≥1x per week and/or requiring blood transfusions) attributed to CRP at colonoscopy

iii. had no constant requirement for medications likely to influence anorectal motility such as opioid analgesics and anti-diarrhoeal agents

iv. Had provided signed informed consent

2.3.2 Experimental protocol

The 30 eligible patients were randomized to treatment with APC (n = 17) or topical formalin (n = 13).

Each patient underwent evaluations of (i) anorectal symptoms (validated questionnaires including modified LENT-SOMA scales for GI symptoms and visual analogue scales for rectal bleeding), (ii) anorectal motor and sensory function (manometry with a perfused sleeve and multiport assembly incorporating a highly compliant polyethylene bag in the rectum) and (iii) anal sphincteric morphology (endoanal ultrasound) before and after the treatment endpoint (defined as reduction

	Normal	Patients	*p*-Value
RD 10			
Anal 0.5 cm†	47.3 ± 10.8	27.7 ± 4.1	0.05
Sleeve	41.6 ± 7.9	30.8 ± 4.3	0.2
Anorectal 4 cm†	8.6 ± 1.5	8.1 ± 0.6	0.77
RD 20			
Anal 0.5 cm*	40.2 ± 5.9	24.6 ± 3.0	0.02
Sleeve	34.2 ± 7.5	26.7 ± 3.4	0.31
Anorectal 4 cm†	10.4 ± 1.9	9.1 ± 0.7	0.44
RD 40			
Anal 0.5 cm†	35.6 ± 4.8	23.1 ± 3.2	0.04
Sleeve	30.2 ± 4.7	30.3 ± 3.7	0.99
Anorectal 4 cm†	12 ± 1.7	10.2 ± 0.8	0.3
RD 60			
Anal 0.5 cm†	43.5 ± 12.0	29.9 ± 7.6	0.33
Sleeve	31.1 ± 6.0	30.9 ± 4.0	0.98
Anorectal 4 cm†	17 ± 2.5	12.8 ± 1.3	0.12
RD 100			
Anal 0.5 cm†	43.8 ± 11.8	20.1 ± 6.3	0.09
Sleeve	30.5 ± 6.9	35.5 ± 5.7	0.59
Anorectal 4 cm†	13.7 ± 2.5	19 ± 6.6	0.49

**Data are mean values ± SEM.*

†Manometric port distances from anal verge.
From Yeoh et al. [14], with permission.

Table 5.
*Residual anorectal pressures in response to rectal distension (RD), with 10 ml, 20 ml, 40 ml, 60 ml and 100 ml**

of rectal bleeding to 1x per month or better, reduction of visual analogue scales to ≤25 mm, no longer needing blood transfusions). Cross-over to the other therapy was allowed if the treatment endpoint was not reached after 4 treatment sessions.

2.3.3 Data presentation and interpretation

Rectal bleeding was controlled in twenty nine of the 30 patients after a median of 2 treatment sessions of APC or topical formalin. One patient, initially treated with APC, failed after 4 treatment sessions but achieved control after 3 sessions of cross-over topical formalin, Control of rectal bleeding was evidenced by reductions of its frequency to ≤1x per month, VAS ≤ 25 mm (**Figures 4** and **5**, **Table 6**) and no further requirement for blood transfusion in the 2 patients (1 each in APC and topical formalin groups) needing this before randomization to therapy.

The durability of control of rectal bleeding by APC and topical formalin was evidenced by only 1 patient in each group needing further therapy after a median (range) follow-up of 111 (29–170) months [15].

No effect on other anorectal symptoms, such as increased frequency and urgency of defecation and fecal incontinence, was observed (**Table 6**).

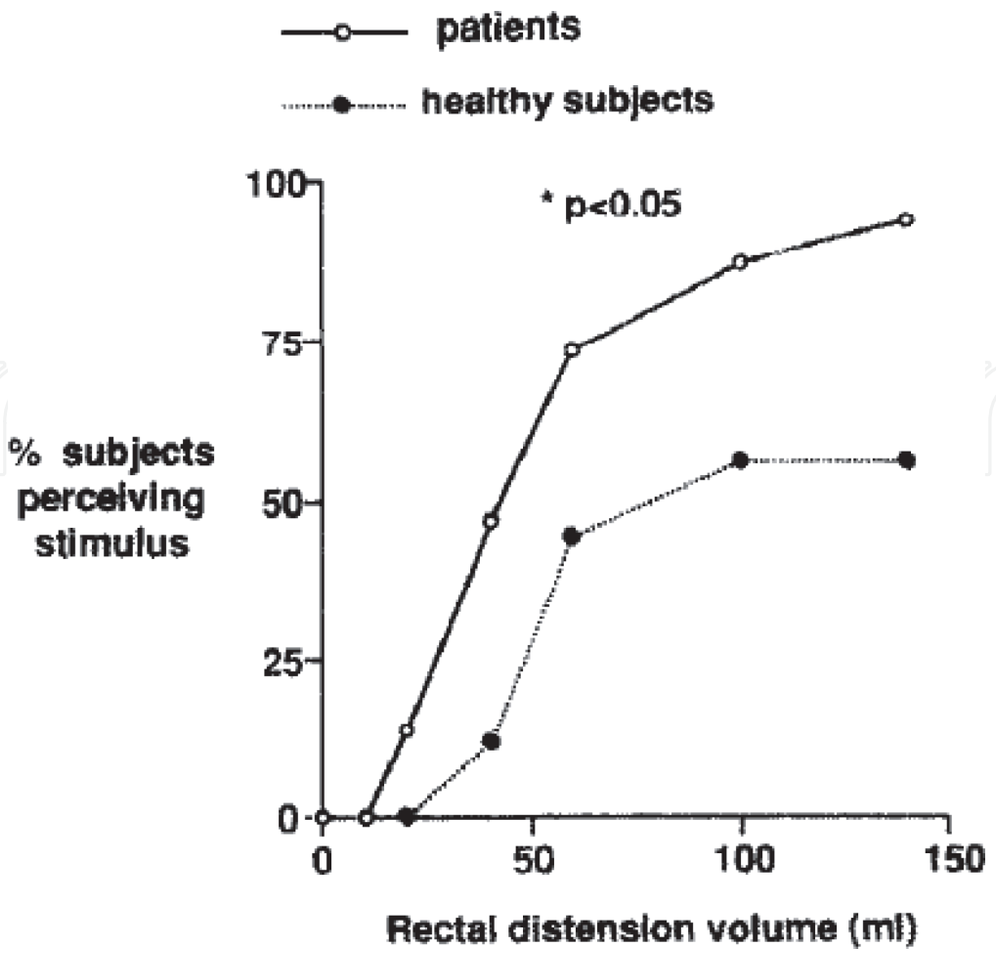

Figure 2.
Rectal volumes at which patients and normal subjects felt desire to defaecate. (From Yeoh et al. [14], with permission).

Other than a reduction in rectal compliance and volumes of sensory perception after APC, no effects on parameters of anorectal function and anal sphincteric morphology were observed (**Table 7**).

APC and topical formalin had comparable efficacy in the durable control of rectal bleeding associated with chronic radiation proctitis but no beneficial effect on anorectal dysfunction.

2.4 Pudendal nerve injury impairs anorectal function and health related quality of life measures ≥2 years after 3D conformal radiotherapy for prostate cancer [16]

2.4.1 Subject selection criteria

The 25 patients, median age = 76 (range 64–83) years, selected for the above study met the following eligibility criteria:

i. Were part of 80 patients still attending follow up ≥2 years after 3D conformal radiotherapy ± high dose rate brachytherapy (HDR) for localized prostate carcinoma under the supervision of the same tertiary institution based Radiation Oncologist

ii. Had no clinical or radiological signs of relapse

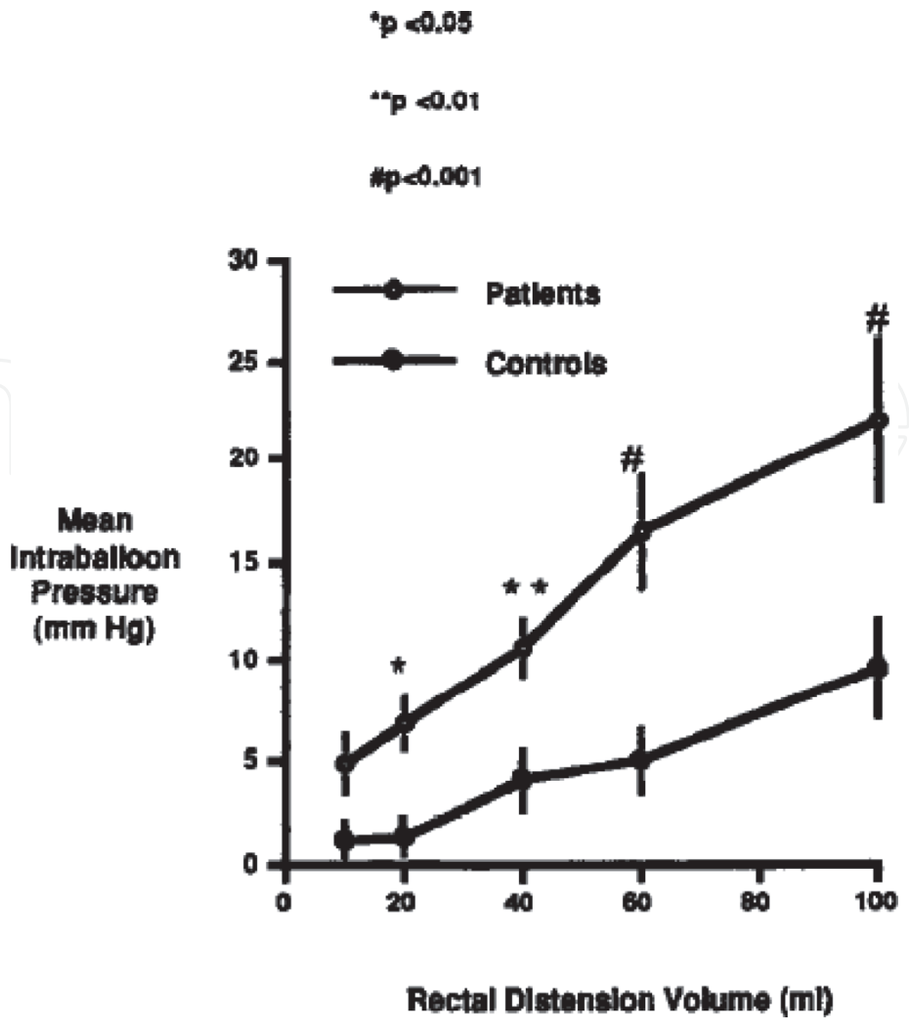

Figure 3.
Pressure/volume relationship in patients and controls associated with rectal distension (from Yeoh et al. [14], with permission).

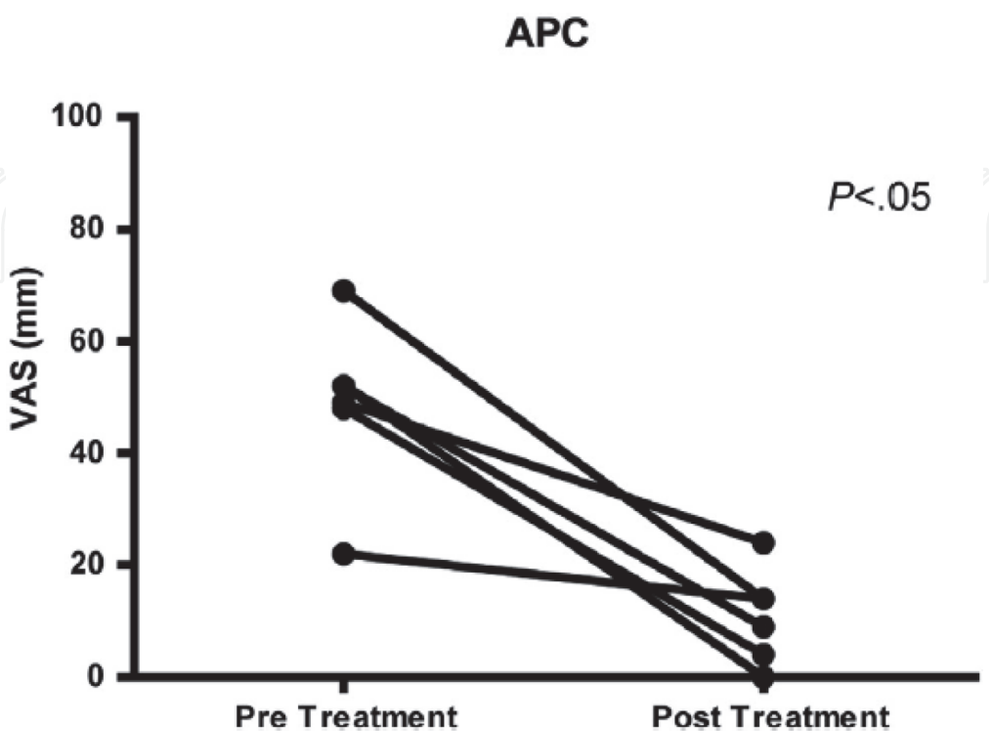

Figure 4.
Visual analogue scale (VAS) before (pre) and after (post) APC treatment. (From Yeoh et al. [15], with permission).

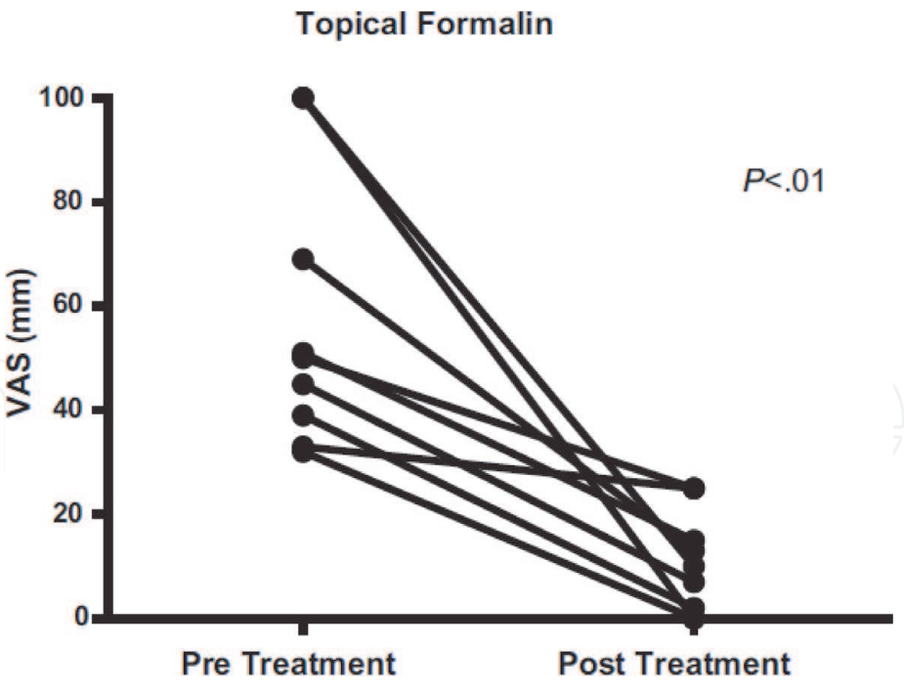

Figure 5.
Visual analogue scale (VAS) before (pre) and after (post) topical formalin treatment. (From Yeoh et al. [15], with permission).

Wilcoxon rank sum test for listed parameters	Before APC	After APC	*P*	Before formalin	After formalin	*P*
No. of bowel actions per week	14(4–39)	16(7–46)	NS	16(3–32)	14(4–42)	NS
Fecal incontinence scores	0(0–10)	0(0–4)	NS	0(0–3)	0(0–2)	NS
Urgency of defecation scores	3(0–6)	4(0–6)	NS	4(0–6)	4(0–6)	NS
Rectal bleeding scores	3(1–4)	1(0–2)	.0001	3(2–4)	1(0–2)	.001
VAS for rectal bleeding (mm)	52(22–75)	14(0–34)	.05	50(32–100)	13(0–25)	.01

Abbreviations: NS, not significant; VAS, visual analogue scale; Values are median (range).From Yeoh et al. [15], with permission.

Table 6.
Effect on anorectal symptom parameters of argon plasma coagulation therapy (APC) and topical formalin treatment.

iii. Had not needed treatment intervention likely to influence anorectal function such as a constant requirement for antidiarrhoeal medication nor argon plasma coagulation therapy (APC) for rectal bleeding

iv. Had provided signed informed consent

Of the 80 patients invited to participate in the study, 48 refused, 7 were ineligible (6 had APC for rectal bleeding, 1 patient had received 2D radiotherapy).

25 age matched patients with localized prostate carcinoma in a recent randomized radiotherapy study served as control subjects [21].

2.4.2 Experimental protocol

Each subject underwent the following evaluations: (i) GI symptoms (modified LENT-SOMA scales), (ii) generic and disease specific HRQoL measures (EORTC

Student's *t* test for listed parameters	Before APC	After APC	*P*	Before formalian	After formalin	*P*
Basal pressure (mm Hg)	52 ± 4	58 ± 2	NS	58 ± 5	51 ± 3	NS
Squeeze pressure (mm Hg)	95 ± 8	100 ± 9	NS	97 ± 6	89 ± 6	NS
Increased intra-abdominal pressure (mm Hg)	85 ± 4	88 ± 6	NS	87 ± 6	92 ± 6	NS
Threshold of perception pressure (mm Hg)	16 ± 1	17 ± 1	NS	18 ± 2	19 ± 2	NS
Threshold of perception volume (mL)	19 ± 2	14 ± 1	.05	17 ± 3	14 ± 1	NS
Desire to defecate (mL)	61 ± 10	48 ± 5	NS	45 ± 11	47 ± 9	NS
Rectal compliance (mm Hg/mL)	4.2 ± 0.4	3.3 ± 0.4	.01	8.1 ± 2.6	4.3 ± 0.7	NS
IAS thickness (mm)	2.4 ± 0.1	2.2 ± 0.1	NS	2.4 ± 0.1	2.4 ± 0.2	NS
EAS thickness (mm)	10.0 ± 0.5	10.5 ± 0.5	NS	11.5 ± 0.6	11.2 ± 0.6	NS

Abbreviations*: NS, not significant; EAS, external anal sphincter; IAS, internal anal sphincter; Values are mean ± SE.From Yeoh et al. [15], with permission.*

Table 7.
Effect on anorectal function and anal sphincteric morphology parameters of argon plasma coagulation therapy (APC) and topical formalin treatment.

QLQ-C30 and EORTC QLQ-PR25 questionnaires), (iii) anorectal motor and sensory function (manometry with a perfused sleeve and multiport assembly incorporating a highly compliant polyethylene bag in the rectum), (iv) pudendal nerve function (terminal motor nerve latency) and (v) anal sphincteric morphology (endoanal ultrasound).

The data of the 25 patients ≥2 years after 3D conformal radiotherapy for prostate cancer were compared with the before radiotherapy (baseline) data of the 25 control subjects.

The data of symptomatic (defined as patients with Total LENT-SOMA GI symptom scores ≥5, n = 13) and asymptomatic (defined as patients with Total LENT-SOMA GI symptom scores ≤4, n = 12) patients among the 25 patients ≥2 years after 3D conformal radiotherapy were also compared.

2.4.3 Data presentation and interpretation

2.4.3.1 Comparisons of modified LENT-SOMA GI symptoms and EORTC HRQoL measures

Patients in this study had significantly higher modified LENT – SOMA frequency and urgency of defaecation, rectal bleeding and mucous discharge scores ≥2 years after 3D conformal radiotherapy compared to the age matched control subjects before radiotherapy (**Table 8**). The patients also had worse (lower) EORTC QLQ-C30 cognitive functioning scores and worse (higher) EORTC QLQ-PR25 bowel symptom scores compared to the controls before radiotherapy (**Table 8**).

Symptomatic patients had significantly higher (i) modified LENT SOMA urgency of defaecation and rectal bleeding scores and (ii) EORTC QLQ-PR25 bowel and urinary symptom scores compared with asymptomatic patients (**Table 9**). Symptomatic patients also had worse (lower) EORTC QLQ-C30 social and emotional functional as well as global health scores compared to asymptomatic patients (**Table 9**).

LENTSOMA	Whole Patient Group	Age Matched Patient Group	p value
Frequency	1 (0–3)	0 (0–1)	<0.01
Diarrhea	0 (0–2)	0 (0–1)	ns
Pain	0 (0–2)	0 (0–2)	ns
Mucous	0 (0–3)	0 (0–1)	<0.05
Urgency	2 (0–4)	1 (0–2)	<0.001
Bleeding	0 (0–3)	0 (0–0)	<0.0001
EORTC HRQoL QLQ-C30			
Physical Functioning	100 (60–100)	93 (47–100)	ns
Role Functioning	100 (50–100)	100 (17–100)	ns
Emotional Functioning	83 (58–100)	83 (67–100)	ns
Cognitive Functioning	83 (50–100)	83 (67–100)	<0.05
Social Functioning	100 (50–100)	100 (33–100)	ns
Global Health Status	83 (17–100)	83 (33–100)	ns
Dyspnoea	0 (0–33)	0 (0–100)	ns
Insomnia	33 (0–100)	33 (0–100)	ns
Appetite Loss	0 (0–33)	0 (0–33)	ns
Nausea And Vomiting	0 (0–17)	0 (0–33)	ns
Constipation	0 (0–67)	0 (0–67)	ns
Diarrhea	0 (0–100)	0 (0–33)	ns
Fatigue	22 (0–44)	22 (0–78)	ns
Pain	0 (0–100)	0 (0–100)	ns
Financial Difficulty	0 (0–33)	0 (0–67)	ns
EORTC QLQ-PR25			
Urinary Symptoms	17 (0–58)	13 (0–67)	ns
Bowel Symptoms	8 (0–42)	0 (0–17)	<0.01
Hormonal Treatment-Related Symptoms	6 (0–50)	6 (0–50)	ns

Abbreviations*: ns, not significant; LENT-SOMA, late effect normal tissue – subjective objective management analytic; EORTC, European Organization for Research and Treatment of Cancer; QLQ, quality of life questionnaire; Values are median (range).From Yeoh et al. [16], with permission.*

Table 8.
Comparison of modified LENT-SOMA GI symptoms and EORTC generic (QOL-C30) and disease specific (QLQ-PR25) HRQoL data between whole patient group and age matched patients before radiotherapy.

2.4.3.2 Comparisons of anorectal and pudendal nerve function data and anal sphincter morphology measurements

All parameters of anorectal motor and sensory function except for threshold volumes for sensory perception were significantly worse ≥2 years after 3D conformal radiotherapy compared to age matched control subjects before radiotherapy (**Table 10**).

Unilateral and/or bilateral pudendal nerve responses were delayed in 13/24 (54%) of the patients compared to only 2/20 (10%) aged matched controls before radiotherapy ($p < 0.0001$, data not shown).

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 of 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

Abbreviations*: ns, not significant; LENT-SOMA, late effect normal tissue – subjective objective management analytic; EORTC, European Organization for Research and Treatment of Cancer; QLQ, quality of life questionnaire; Values are median (range).From Yeoh et al. [16], with permission.*

Table 9.
Comparison of modified LENT-SOMA GI symptoms and EORTC generic (QOL-C30) and disease specific (QLQ-PR25) HRQoL data between symptomatic and asymptomatic patients.

The thickness of both IAS and EAS was significantly less in the patients compared to the control subjects before radiotherapy (**Table 10**).

Fecal incontinence scores were worse in the symptomatic compared to the asymptomatic patients but no differences were detected in thickness of either IAS or EAS in the patient sub-groups (**Table 11**).

Unilateral and/or bilateral pudendal nerve responses were delayed in 9/13 (69%) of symptomatic compared to only 4/11 (36%) of asymptomatic patients ($p < 0.0001$, data not shown).

Rectal and anal (i) V40Gy > 65%, (ii) Dmax >60 Gy, (iii) pudendal nerve Dmax >60 Gy and (iv) Anal V60 Gy >40% were associated with a greater prevalence of pudendal nerve function [16].

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

Abbreviations*: ns, not significant; IAS, internal anal sphincter; EAS, external anal sphincter; FI, fecal incontinence; Values are mean ± SE.From Yeoh et al. [16], with permission.*

Table 10.
Comparison of anorectal function and anal sphincter morphology data between whole patient group and age matched patients before radiotherapy.

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

Abbreviations*: ns, not significant; IAS, internal anal sphincter; EAS, external anal sphincter; FI, fecal incontinence; Values are means ± SE.From Yeoh et al. [16], with permission.*

Table 11.
Comparison of anorectal function and anal sphincter morphology data between symptomatic and asymptomatic patients.

3D radiotherapy ± high dose rate brachytherapy (HDR) for localized prostate carcinoma impairs functional measures including HRQoL, anorectal and pudendal nerve function ≥2 years after treatment. Radiation dose constraints are proposed for reducing the prevalence of pudendal nerve dysfunction.

3. Implications and summary of findings of studies and conclusion(s)

The data presented in this chapter, based on studies spanning over two decades examining gastrointestinal effects of pelvic radiotherapy for prostate and

gynecological cancer, indicate that despite advances in radiotherapy technology, anorectal dysfunction persist or progressively worsen over a period of 5–10 years after treatment. The multiple deteriorations in anorectal function, consisting of weakness of the anal sphincters, stiffness of the rectal wall and consequent increase in rectal sensitivity, result in ~50% of patients being housebound and only able to go out if there is a toilet nearby. The studies also show that the prevalence of rectal bleeding is half that of urgency of defaecation. In addition, results of the first randomized trial of Argon Plasma Coagulation Therapy versus topical formalin for intractable rectal bleeding after radiotherapy for prostate cancer indicate that durable control is achieved in 94–100% of patients after a median of 2 sessions of either treatment, only 7% of patients requiring re-treatment after a median follow-up of 9 years [15]. In contrast, therapeutic options for anorectal dysfunction are limited to medications such as loperamide and nicardipine based on pathophysiological evaluation of bowel disorders which include chronic radiation proctitis. For example, nicardipine which increases the rectal threshold for desire to defecate in patients with irritable bowel syndrome and reported to be effective in the treatment of urgency of defecation has been proposed for the treatment of urgency of defecation associated with chronic radiation proctitis since threshold volumes for desire to defecate are also reduced in CRP [14]. Similarly, loperamide, by increasing basal anal and squeeze pressures in patients with fecal incontinence of diverse aetiologies including radiation bowel disease, has been proposed for the treatment of fecal incontinence associated with CRP [14]. However, loperamide reduces stool bulk potentially increasing the risk of rectal bleeding and a lower dose than that prescribed for other bowel disorders is recommended [2]. Whilst the most advanced radiation treatment technique of intensity modulated radiation therapy (IMRT) was not used in the studies here, the prevalence of anorectal toxicity after IMRT for prostate cancer has been reported to be 65%, worse or no different from that reported in studies using less advanced treatment techniques including those

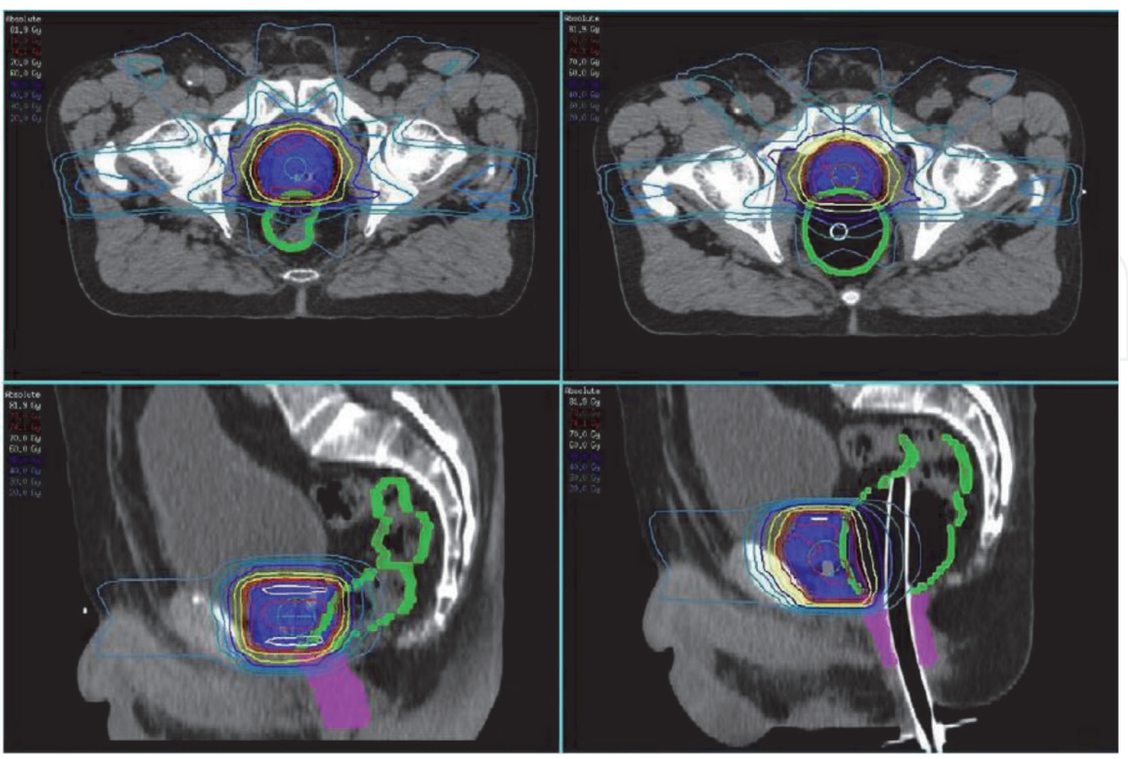

Figure 6.
Transverse (top) and sagittal dose distributions of IMRT plans for prostate cancer without (left) and with (right) endorectal balloon in place. Contours: Rectal wall (green), anal wall (purple). (From Smeenk et al. [5], with permission).

reported here [1, 2, 6, 14, 16]. A likely explanation for the failure of IMRT to reduce anorectal dysmotility after treatment is that its underlying pathogenesis is damage to neural tissue in the bowel wall and/or the pudendal nerves [2, 16]. As discussed in the editorial accompanying the published findings of the final study of this chapter [19], the pudendal nerves are not considered as normal tissues at risk of radiation damage and therefore could potentially receive the same if not higher doses of radiation as the prostate target of irradiation. Radiation dose constraints for normal tissues at risk including the pudendal nerves have been proposed (Section 2.4 above) and if applied now that IMRT has been adopted almost universally, patients who need pelvic radiotherapy for urological and gynecological cancer can look forward to a future free of distressing bowel morbidity. Furthermore, the daily insertion of endorectal balloons during radiotherapy (**Figure 6**), which have been shown to be very well tolerated and to further reduce radiation exposure of the rectal and anal wall (and the anatomically closely related pudendal nerves) by IMRT [5] means a bowel complication free cure of pelvic malignant disease can be realistically achieved in the foreseeable future.

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The names of the contributors to the 4 published studies, listed as co-authors in the references section, are acknowledged although none of these co-authors contributed to the writing of this chapter.

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References

[1] Andreyev HJN. Gastrointestinal problems after pelvic radiotherapy: Th past, the present and the future. Clin Oncol (R Coll Radiol) 2007); 19: 790-799.

[2] Yeoh EK, Holloway RH, Fraser RJ et al. Pathophysiology and natural history of anorectal sequelae following radiation therapy for carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2012; 84(5):e593-e599.

[3] Krol R, Smeenk RJ, van Lin ENJT, Hopman WPM. Impact of late anorectal dysfunction on quality of life after pelvic radiotherapy. Int J Colorectal Dis 2013; 28(4):519-526.

[4] Lawton CA, Won M, Pilepich MV et al. Long term treatment sequelae following external beam radiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. Int J Radiat Oncol Biol Phys 1991; 21:935-939.

[5] Smeenk RJ, Teh BS, Butler B, van Lin ENJT, Kaanders JHAM. Is there a role for endorectal balloons in prostate radiotherapy? A systematic review. Radiother Oncol 2010; 95:277-282.

[6] Putta S, Andreyev HJN. Faecal Incontinence: A late side-effect of pelvic radiotherapy. Clin Oncol (R Coll Radiol) 2005); 17:469-477.

[7] Denham JW, O'Brien PC, Dunstan RH et al. Is there more than one late radiation proctitis syndrome? Radiother Oncol 1999; 51:43-53.

[8] Franklin CIV, Parker CA, Morton KM. Late effects of radiation therapy for prostate carcinoma: the patient's perspective of bladder, bowel and sexual morbidity. Aust Radiol 1998; 42:58-65.

[9] Widmark A, Fransson P, Tavelin B. Self-assessment questionnaire for evaluating urinary and intestinal late side effects after pelvic radiotherapy in patients with prostate cancer compared with an age-matched control population. Cancer 1994; 74:2520-2532.

[10] Varma JS, Smith AN, Busuttil A. Function of the anal sphincters after chronic radiation injury. Gut 1986; 27: 528-533.

[11] Yeoh EK, Holloway RH, Fraser RJ et al. Anorectal function after three versus two-dimensional radiation therapy for carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2009; 73: 46-52.

[12] Yeoh EK, Holloway RH, Fraser RJ et al. Anorectal dysfunction increases with time following radiation therapy for carcinoma of the prostate. Am J Gastroenterol 2004; 99:361-369.

[13] Yeoh EK, Holloway RH, Fraser RJ et al. Hypofractionated versus conventionally fractionated radiation therapy for prostate carcinoma: updated results of a Phase III randomized trial. Int J Radiat Oncol Biol Phys 2006; 66: 1072-1083.

[14] Yeoh E, Sun WM, Russo A, Ibanez L, Horowitz M. A retrospective study of pelvic irradiation for gynaecological cancer on anorectal function. Int J Radiat Oncol Biol Phys 1996; 35(5):1003-1010.

[15] Yeoh E, Tam W, Schoeman M et al. Argon Plasma Coagulation Therapy versus Topical Formalin for intractable rectal bleeding and anorectal dysfunction after radiation therapy for prostate carcinoma. Int J Radiat Oncol Biol Phys 2013; 87(5):954-959.

[16] Yeoh E, Botten R, Di Matteo A et al. Pudendal nerve injury impairs anorectal function and health related quality of life measures ≥2 years after 3D

conformal radiotherapy for prostate cancer. Acta Oncologica 2018; 57(4): 456-464.

[17] Krol R, Hopman WPM, Smeenk RJ, van Lin ENJT. Increased recta wall stiffness after prostate radiotherapy: relation with faecal urgency. Neurogastroenterol Motil 2011; 24(4): 339-E166.

[18] Yeoh EK, Bartholomeusz, Holloway RH et al. Disturbed colonic motility contributes to anorectal symptoms and dysfunction after radiation therapy for prostate carcinoma. Int J Radiat Oncol Biol Phys 2010; 78:773-780.

[19] Steineck G, Bull C, Sjoberg F. Contouring pudendal nerves. Editorial. Acta Oncologica 2018; 57(4):438-439.

[20] Yeoh EK, Horowitz M, Russo A et al. Effect of pelvic irradiation on gastrointestinal function: A prospective longitudinal study. Am J Med 1993; 95: 397-406.

[21] Botten RJ, Di Matteo AC, Sharma KG et al. Endorectal balloon during image guided radiation therapy for carcinoma of the prostate reduces long term radiation induced rectal bleeding and subsequent Argon Plasma Coagulation Treatment. Gastroenterology 2019; 156(6):S353-S354.