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Original Article

Impact of radiotherapy on anorectal function in patients with rectal cancer following a watch and wait programme

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ABSTRACT

Background and purpose: To assess the long-term anorectal function in rectal cancer patients following a watch-and-wait policy after chemoradiotherapy and to investigate the dose–volume effects of radiotherapy on the anorectal function.

Methods and materials: Thirty-three patients with primary rectal cancer who were treated with chemoradiotherapy and a watch-and-wait policy with minimum follow-up of 2 years were included. We assessed the anorectal function using anorectal manometry and patient reported outcomes (Vaizey and LARS score). Dose–volume histograms were calculated for the rectum and anal sphincter complex, and associations between the dose–volume parameters and anorectal function were assessed.

Results: D_{mean} to the rectum and anal sphincter complex was 50.5 Gy and 44.7 Gy, respectively. After a median follow-up of 38 (range 23–116) months, 33.3% of the patients reported major LARS. Mean LARS score was 23.4 ± 11.3 and mean Vaizey score was 4.3 ± 4.1. The most frequent complaints were clustering of defaecation and faecal urgency. Trends towards a higher Vaizey and LARS score after higher anal sphincter complex dose were observed, although these associations were not statistically significant.

Conclusions: This is the first study to investigate the late dose-volume effects of radiotherapy specifically on the anorectal function in rectal cancer patients. One-third of the patients had major LARS and the most frequent reported complaints were clustering and faecal urgency. Additionally, we observed trends towards worse long-term anorectal function after higher anal sphincter complex radiotherapy dose. However, this should be evaluated on a larger scale. Future efforts to minimise the dose to the sphincters could possibly reduce the impact of radiotherapy on the anorectal function.

The standard of care for patients with locally advanced or distal rectal cancer is neoadjuvant chemoradiation therapy (CRT) followed by total mesorectal excision (TME). CRT leads to downsizing and downstaging of the tumour in most patients, it may increase the opportunity for sphincter-saving surgery and CRT decreases the risk for local recurrence [1]. However, treatment with neoadjuvant CRT and TME can adversely affect bladder, sexual, and anorectal function in the long term [2]. In patients who achieve a complete response to neoadjuvant CRT, a watch-and-wait policy can be considered to avoid the related morbidity and mortality of TME [3–5].

The main goal of a watch-and-wait policy is an anticipated improved functional outcome and quality of life, while maintaining a good oncological outcome. While there is growing evidence supporting the oncological safety, the quality of life and functional outcomes after a watch-and-wait policy remain less explored. In a previous report [6] we showed that quality of life after a watch-and-wait policy was better than after CRT and TME. Nonetheless, the anorectal function was impaired in the watch-and-wait group, with one third of the patients reporting major bowel dysfunction. This comes as no surprise as irradiation of the rectum is known to cause injury to the rectal wall and related autonomic nerves resulting in impaired long-term functional outcome [7]. Because of the proximity of the anal canal to the tumour, the anal sphincter muscles are often also in the high-dose field of radiation in patients with low rectal cancer. However, very limited data are available on the relationship between radiotherapy dose and anorectal dysfunction in rectal cancer patients. Particularly in rectal cancer patients in whom no resection is performed after CRT, e.g. in patients following a watch-and-wait policy, the effects

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of chemoradiotherapy alone on functional outcomes can be assessed. In this study we assessed the long-term anorectal function in rectal cancer patients following a watch-and-wait policy, using the Vaizey score, LARS (Low Anterior Resection Syndrome) score and anorectal manometry. Additionally, we explored the associations between the radiotherapy dosimetric parameters of the rectum and anal sphincter complex and the anorectal function outcomes.

Methods and material

Study population

Patients with primary rectal cancer and a complete response after CRT who were treated according to a watch-and-wait policy in our institute between January 2009 and April 2015 and who had a minimum follow-up of two years were included in this cross-sectional study. Follow-up of ≥ two years was chosen so long-term effects, which at that time are expected to have reached a plateau phase, could be measured. All patients were part of a prospective cohort study on the watch-and-wait policy (clinicaltrials.gov NCT00939666) and a part was also included in a previous report on quality of life [6]. The inclusion criteria for a watch-and-wait policy in rectal cancer have been described previously [4,8]. Exclusion criteria for the present study were salvage therapy for recurrent disease or having a colostomy. Ethics committee approval was obtained for sending out questionnaires and patients gave a separate informed consent for a manometric evaluation of the anorectal function during routine follow-up.

Chemoradiotherapy

All patients were treated with chemoradiotherapy. 3D-conformal or intensity-modulated radiotherapy consisted of 50.4 Gy, with daily fractions of 1.8 Gy on weekdays. Dose specification occurred according to ICRU 50/62. The clinical target volume (CTV) included the gross tumour volume, the mesorectum, presacral and internal iliac node regions, and in case of distal node positive tumours the obturator fossa. A symmetric PTV margin of 1 cm was applied. No dose limitations were used for the anal sphincter complex during initial treatment planning. Radiotherapy was combined with 825 mg/m^2/day capecitabine bid, seven days a week.

Organ delineation and dose calculations

The rectum and anal sphincter complex were manually delineated on the axial CT images (3 mm slice thickness) of the original radiotherapy planning CT scans, using Focal™ treatment planning system (XiO, Elekta AB, Stockholm, Sweden). Organ contours were defined according to the Pelvic Normal Tissue contouring guidelines by the Radiation Therapy Oncology Group (RTOG) [9]. The rectum was defined as a solid organ including the rectal contents from the lowest slice with a rectal lumen to the rectosigmoid flexure where the rectum moves ventrally and loses its round shape. The anal sphincter complex (internal and external sphincter muscle) circumference was delineated as a solid organ from anal verge to the anorectal border. All delineations were performed by one investigator (M.S.) and confirmed by a radiation oncologist specialised in rectal cancer treatment (M.B.). Examples of these delineations are shown in Fig. 1.

Dose–volume histograms (DVH) were calculated with the original treatment plans and were used to measure the radiation dosimetric coverage of the rectum and anal sphincter complex for each patient. The maximum and mean doses were calculated

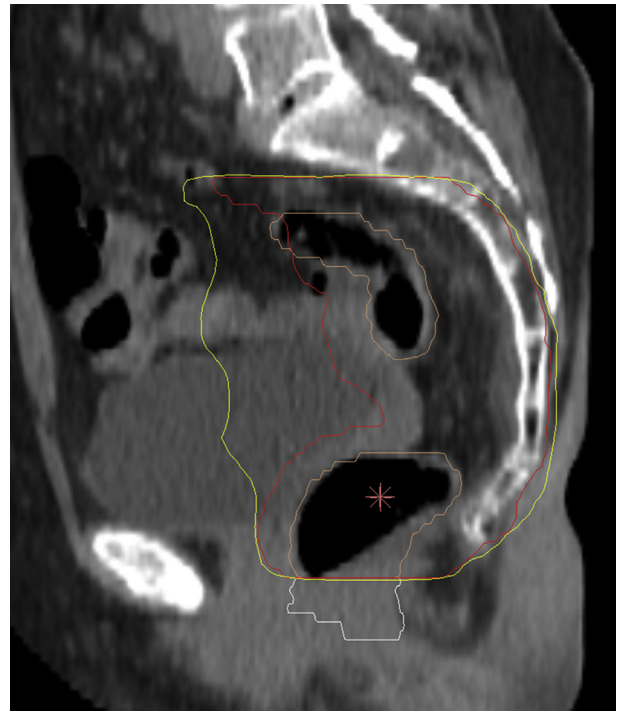

Fig. 1. Delineation of anal sphincter complex (white) and rectum (orange) on CT scan. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(D_{max} and D_{mean}), as well as the relative volumes receiving a dose of 30–50 Gy or more ($V_{30\ Gy}$-$V_{50\ Gy}$).

Manometry

Anorectal function was assessed using manometry at one of the routine follow-up outpatient visits. Anorectal manometry was performed with the patient in the left lateral position with knees and hips bent to 90°. Patients did not receive bowel preparation [10]. A four-channel catheter (Mui Scientific, Mississauga, Canada) with a water perfusion system connected to an electronic polygraph (Synectics Medical, Stockholm, Sweden) was used for the investigation. A 7 cm inflatable balloon was incorporated at the top of the catheter. The catheter was calibrated outside the patient at study level before introduction. A stationary technique was used and mean anal resting pressure (MRP) and squeeze anal pressures (MRP) were measured [11]. These parameters were calculated as the average of the four radial measuring points. For rectal capacity, first rectal sensation (FS), volume at first urge to defaecate (FUTD) and maximum tolerable volume (MTV) were measured during stepwise balloon inflation. Manometry examinations were performed by two investigators (M.S. and B.H.).

Questionnaires

Anorectal function was also evaluated using two validated scores sent out as questionnaires: the Vaizey score and LARS score.

The Vaizey score was used to assess faecal incontinence [12]. Patients were asked to evaluate their defaecation pattern in the last four weeks, including questions regarding consistency of stool loss, frequency and its effect on lifestyle. Results are reported on a continuous scale from 0 to 24. Faecal incontinence is defined as a score ≥12 points.

The Dutch version of the LARS score was used to evaluate bowel dysfunction [13]. It consists of five questions regarding incontinence for flatus and liquid stool, frequency, clustering and urgency.

The range of this score is 0–42 and outcome categories are no LARS (score 0–20), minor LARS (score 21–29) and major LARS (score 30–42).

Statistical analysis

SPSS v22.0 (SPSS Inc, Chicago, IL) was used for statistical analyses. Stochastic regression imputation was used to impute incomplete variables to prevent a loss of statistical precision and to decrease the likelihood of bias. Multiple regression was used to quantify preliminary associations between the dose–volume parameters and the manometry and questionnaire scores and was adjusted for sex, tumour height and age. A two-tailed p value $\leq$0.05 was considered significant in all analyses.

Results

Patient characteristics and dosimetric data

Thirty-three patients with a median age of 68 (range 38–85) years, of whom 21 male (64%), were included in this study. Patients' demographics are shown in Table 1. Median time from end of CRT to anorectal function assessment was 38 (range 23–117) months. Twenty-three patients (70%) had low rectal cancer ($\leq$5 cm from anorectal junction), 10 patients had mid-high rectal cancer. Mean (±SD) distance from distal border of tumour to anorectal junction was 3.9 (±3.0) cm.

The radiation dose–volume data are shown in Table 2. The mean (±SD) D_{mean} and mean $V_{50\ Gy}$ to the rectum were 50.5 ± 1.3 Gy and 90.1 ± 19.4%, respectively. The mean (±SD) D_{mean} to the anal sphincter complex was 44.7 ± 9.7 Gy, whereas the $V_{50\ Gy}$ was 47.1% ± 37.9%, meaning that on average 47% of the anal sphincter volume had a planned dose of $\geq$50 Gy.

Table 1
Patients' demographics (n = 33).

Characteristics	
Sex	
Male	21 (63.6%)
Female	12 (36.4%)
Median age, in years (range)	67.5 (38–85)
Median follow-up, in months (range)	38.4 (23–117)
cT stage	
cT2	8 (24.2%)
cT3	24 (72.8%)
cT4	1 (3.0%)
cN stage	
cN0	8 (24.2%)
cN1	12 (36.4%)
cN2	13 (39.4%)
Tumour height	
$\leq$5 cm	23 (69.7%)
>5 cm	10 (30.3%)

Table 2
Radiation dose–volume data.

	Anal sphincter complex	Rectum
Volume (cm^3)	14.9 ± 4.7	98.0 ± 27.7
D_{max} (Gy)	47 ± 11	52.0 ± 1.1
D_{mean} (Gy)	44.7 ± 9.7	50.5 ± 1.3
$V_{30\ Gy}$ (%)	85.4 ± 25.3	99.2 ± 2.7
$V_{35\ Gy}$ (%)	85.0 ± 25.6	98.8 ± 2.8
$V_{40\ Gy}$ (%)	81.3 ± 27.2	99.1 ± 2.7
$V_{45\ Gy}$ (%)	80.3 ± 28.4	99.0 ± 3.1
$V_{50\ Gy}$ (%)	47.1 ± 37.9	90.1 ± 19.4

Abbreviations: D_{max} = Maximal dose, D_{mean} = Mean dose, $V_{30\ Gy}$-$V_{50\ Gy}$ = percentage of volume receiving >30 to >50 Gy.

Manometry

Overall, the mean MRP was 30 ± 12 mmHg and mean MSP was 104 ± 41 mmHg. Mean volume at first sensation (FS) was 47 ± 26 mL, 88 ± 28 mL at first urge to defaecate (FUTD), and 136 ± 36 mL at maximum threshold (MTV), see Table 3.

Questionnaire outcomes

The mean Vaizey score was 4.3 ± 4.1. Two (6%) patients had faecal incontinence, based on the Vaizey score (>12 points). The results for all items on the Vaizey score are presented in Table 4. Of the 33 patients, 15 (46%) patients reported a lack of the ability to defer defaecation for 15 minutes. One (3%) patient reported the use of pads/plugs, and one (3.0%) other patient reported the use of constipating agents.

The mean LARS score was 23.4 ± 11.3. Twelve (36%) patients had no LARS (score 0–20), 10 (30%) patients had minor LARS (score 21–29) and 11 (33%) patients had major LARS (score 30–39). The most reported complaint in the LARS questionnaire was clustering, with nine (27%) patients reporting clustering at least once a week and 18 patients (55%) less than once a week. Urge incontinence for faeces at least once a week was reported by 15 (46%) patients and less than once a week by 9 (27%) patients. Occasions of uncontrollable flatus at least once a week were reported in 10 (30%) patients, less than one a week in 8 (24%) patients. Complaints of frequency or accidental leakage of stools were less often reported, see Fig. 2.

Correlation of dosimetric data to anorectal function

There weren't any statistically significant associations between dose parameters and the LARS or Vaizey score. However, we did observe a trend towards higher Vaizey scores after higher D_{max} (β = 0.341, p = 0.211), $V_{30\ Gy}$ (β = 0.374, p = 0.095), $V_{35\ Gy}$ (β = 0.343, p = 0.126) and $V_{40\ Gy}$ (β = 0.381, p = 0.109) of the anal sphincter complex. Additionally, a trend towards higher LARS scores after higher D_{mean} of the anal sphincter complex (β = 0.362, p = 0.122) was observed. Regarding the rectal dose, regression analysis showed trends towards higher Vaizey scores after higher $V_{35\ Gy}$ (β = 0.353, p = 0.066) and $V_{40\ Gy}$ (β = 0.309, p = 0.117), although not statistically significant. The results of all regression analyses are presented in Appendix 1.

For all dosimetric parameters of the anal sphincter complex, except $V_{50\ Gy}$, higher doses were associated with higher squeeze pressure (MSP). No associations were found between the dosimetric parameters and resting pressure (MRP) or anorectal sensory function (FS, FUTD, MTV).

Discussion

This study assessed the long-term anorectal function and the association between the anorectal function and the radiotherapy dose parameters in rectal cancer patients following a watch-and-wait policy. One-third of the patients has major LARS after a minimal follow-up of two years. The most frequent complaints were clustering of defaecation and faecal urgency. Additionally, we observed trends towards worse long-term anorectal function after higher anal sphincter complex radiotherapy dose.

To date, there have been few studies that assessed the anorectal function in rectal cancer patients treated according to a watch-and-wait policy after CRT. In our previous study by Hupkens et al. [6], the long-term quality of life and functional outcomes were compared between 41 watch-and-wait patients and 41 patients treated with CRT and TME. In that study, 36% of the

Table 3
Vaizey score items ($n = 33$).

	Never	Rarely	Sometimes	Weekly	Daily
Incontinence for solid stool, *n* (%)	28 (85)	– (0)	4 (12)	– (0)	1 (3)
Incontinence for liquid stool, *n* (%)	21 (64)	7 (21)	4 (12)	1 (3)	– (0)
Incontinence for gas, *n* (%)	13 (40)	11 (33)	5 (15)	1 (3)	3 (9)
Alterations in lifestyle, *n* (%)	27 (81)	3 (10)	2 (6)	– (0)	1 (3)
	No	Yes			
Need to wear a pad/plug, *n* (%)	32 (97)	1 (3)			
Use of constipating agents, *n* (%)	32 (97)	1 (3)			
Unable to defer defaecation for 15 min, *n* (%)	17 (54)	15 (46)			

Table 4
Results of anorectal manometry.

	$n = 33$
MRP, mean (SD) mmHg	30 (12)
MSP, mean (SD), mmHg	104 (41)
FS, mean (SD), mL	47 (26)
FUTD, mean (SD), mL	88 (28)
MTV, mean (SD), mL	136 (36)

Abbreviations: MRP = mean resting pressure, MSP = mean squeeze pressure, FS = volume to first sensation, FUTD = volume to first urge to defecate, MTV = maximum tolerable volume.

watch-and-wait policy patients experienced major LARS, compared to 67% of the patients who underwent CRT followed by TME. This showed that although bowel function was generally better after a watch-and-wait policy, there were patients with significant functional impairment after CRT alone.

Habr-Gama et al. on the other hand concluded that the consequences of radiotherapy on the anorectal function may be minimal [14]. The anorectal function of patients undergoing watch-and-wait after CRT to was compared to the function of patients treated with full-thickness local excision after CRT. Fifty-four watch-and-wait patients were assessed with anorectal manometry and validated questionnaires and most outcomes were considered to be within the normal range. However, the Fecal Incontinence Quality of Life (FIQL) Scale and the Vaizey score were used, which both emphasise on faecal incontinence. Although faecal incontinence is a common issue, bowel dysfunction after rectal cancer treatment is more complex and may also involve frequent bowel movements and complaints of clustering and faecal urgency [15]. The scores used in the study of Habr-Gama et al. may not have been sensitive enough to detect these complaints adequately and may therefore have underestimated the adverse effects of radiotherapy.

Despite an absence of baseline anorectal function information in the present study, it is likely that neoadjuvant chemotherapy contributed to the observed bowel dysfunction in this study population as it is well known that neoadjuvant radiotherapy is a risk factor for anorectal dysfunction after TME [16–18]. In other pelvic malignancies, however, it is better established what the effects of stand-alone radiotherapy are on bowel functioning. In anal cancer, approximately 43–54% of the patients report faecal incontinence after radiation treatment [19–21]. In prostate cancer patients, faecal incontinence is reported in up to 57% and bowel urgency in 34% [22,23].

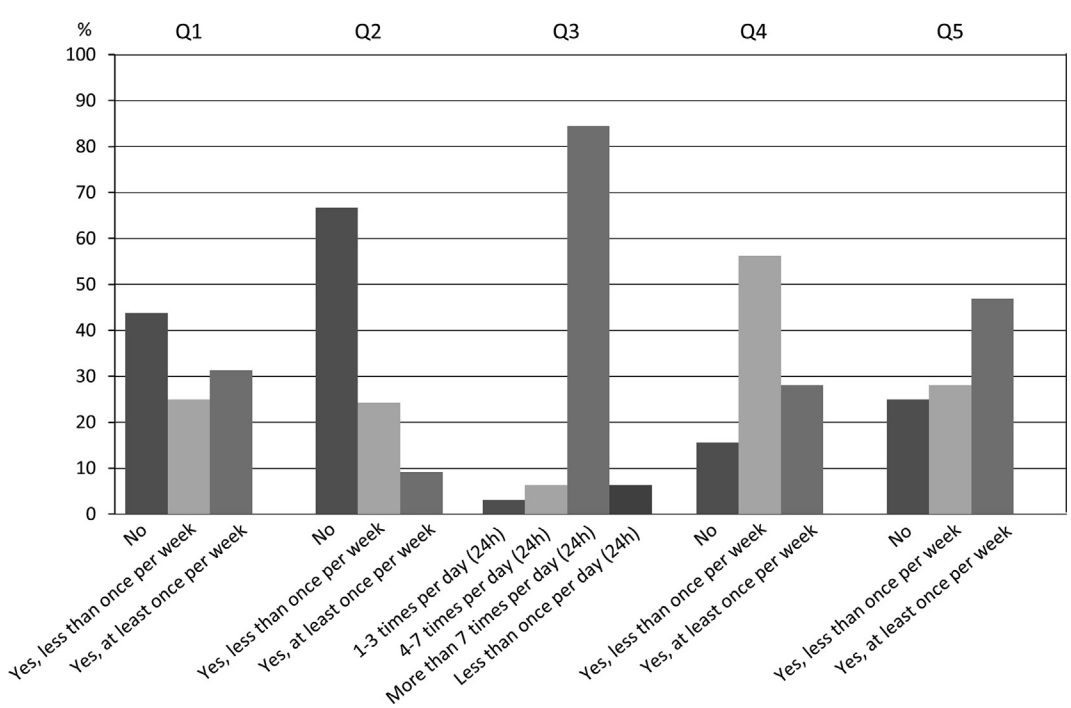

Fig. 2. LARS score; answers per question. Q1: Do you ever have occasions when you cannot control your flatus? Q2: Do you ever have any accidental leakage of liquid stool? Q3: How often do you open your bowel? Q4: Do you ever have to open your bowels again within one hour of the last bowel opening? Q5: Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?

Faecal continence is a complex system and multiple components fundamental to continence are suggested to be involved in the pathogenesis of radiotherapy induced anorectal dysfunction. Some studies suggest that radiotherapy negatively affects innervation of the anorectum, including the pudendal nerve, the myenteric plexus, and the lumbosacral plexus [24–26]. Furthermore radiotherapy can induce structural morphologic alterations, such as collagen depositions in the internal and external anal sphincter [25,27], and fibrosis of the rectal wall [28]. This can compromise sphincter tone, sphincter contractibility, and anorectal sensitivity.

Although we did not find an association between higher planned radiotherapy dose to the anal sphincter complex and lower anal pressures, we did observe low mean anal resting pressures and anal squeeze pressures after CRT in the present study when compared to normal values from literature [29]. This is in accordance with other studies showing reduced anal sphincter tone and squeeze pressures after pelvic irradiation [30–32]. Decreased anal pressures have been related to complaints of urgency and incontinence specifically [33,34]. In prostate cancer, decreased sensory thresholds for defaecation urge have also been reported after irradiation, while in the present study these were in the normal range [30,35].

While there were no significant associations between the dose parameters and questionnaire outcomes, the results suggest that higher Vaizey and LARS score were associated with a higher D_{mean} and D_{max} of the anal sphincter complex, and a higher LARS score with higher D_{mean} of the rectum. One other study in rectal cancer survivors, treated with CRT and TME, investigated the relationship between radiation dose and anorectal function [36]. They showed that the volume of the anal sphincters receiving >20 Gy was predictive of poor sphincter control as measured on the Wexner scale. In prostate cancer survivors, it has repeatedly been shown that dosimetric parameters of the anal sphincter and rectum are associated with late gastro-intestinal toxicity and patient reported outcomes [37–39]. Moreover, the dose to different anatomic substrates have been correlated to different symptoms [33,40]. These studies [33,37–40] suggest that the anorectal region should be avoided whenever possible during radiation treatment planning for prostate cancer. Delineation guidelines and dose constraints for the anal sphincter complex could also facilitate sphincter sparing radiotherapy in rectal cancer, and thereby possibly reduce the impact on functional outcomes.

The following limitations should be taken into consideration when interpreting the results of the present study. Our analyses are based on a relatively small group of patients. As a result, we observed several associations that may be of clinical relevance, but lacked the statistical power to draw firm conclusions. Furthermore, we had no baseline information about the anorectal function, and it remains unclear whether the reported symptoms were present before the diagnosis of rectal cancer and treatment with CRT. However, when baseline measurements are taken in rectal cancer patients, these measurements are likely to be influenced by the rectal tumour and may not represent normal anorectal functioning. In the absence of questionnaires that have been validated specifically for patients undergoing a watch-and-wait policy, we used the LARS score to assess bowel dysfunction.

Despite these limitations, this is the first study to explore the specific dose-volume effects of chemoradiation alone in rectal cancer patients on the long-term anorectal function. Our results may provide support in the rationale for sphincter sparing radiotherapy, however the relation between the dosimetric parameters and the long-term anorectal function in chemoradiation for rectal cancer should be evaluated on a larger scale. Especially with the current interest in radiotherapy to achieve organ preservation in rectal cancer, insights into functional deterioration after radiotherapy are needed, as well as insights into the specific mechanisms that are affected. With these insights, further improvements in radiotherapy delivery could be aided, as to maximise the effect on the tumour while minimising the detrimental impact on the anorectal function.

In conclusion, it is often difficult to differentiate between the radiation and surgery induced damage in rectal cancer patients treated with chemoradiotherapy. This study in rectal cancer patients followed in a watch-and-wait programme is the first study to investigate the dose-volume effects of radiotherapy specifically on the anorectal function in rectal cancer patients. One third of the patients reported major LARS after a minimal follow-up of two years. The most frequent complaints were clustering of defaecation and faecal urgency. Additionally, we observed trends towards worse long-term anorectal function after higher anal sphincter complex radiotherapy dose. However, this should be evaluated on a larger scale. Future efforts to minimise the dose to the sphincters could possibly reduce the impact of radiotherapy on the anorectal function.

Conflicts of interest

All authors had no conflicts of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.11.017.

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