Original article

Effect of radiotherapy for rectal cancer on female sexual function: a prospective cohort study

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Background: **Clinical experience and limited data show that female sexual function is influenced negatively by preoperative radiotherapy (RT) for rectal cancer. The aim of this prospective study was to investigate the impact of RT on sexual function and ovarian reserve measured by levels of anti-Müllerian hormone (AMH).**

Methods: **Women with stage I–III rectal cancer scheduled for surgery with or without preoperative (chemo)RT were included and followed for 2 years. Female Sexual Function Index (FSFI) questionnaire responses and blood samples for hormone analyses, including AMH in women aged 45 years or less, were collected at baseline and during follow-up.**

Results: **In the group of 109 women who received preoperative RT, median scores in all FSFI domains decreased over time, as did the total FSFI score (from 18·5 (range 2·0–36·0) at baseline to 10·8 (2·0–34·8) at 2 years; $P < 0·001$). In the group of 30 women who did not receive preoperative RT, only satisfaction declined over time (from 3·2 (0·8–6·0) to 1·8 (0·8–6·0); $P = 0·012$). In longitudinal regression analysis, the mean decline in FSFI total score was −9·33 (95 per cent c.i. −16·66 to −1·99; $P = 0·013$) for women who had preoperative RT compared with those who did not, with adjustment for age, Psychological General Well-being Index score and relationship with partner. A corresponding association was seen for arousal, lubrication, orgasm and pain. Five of six women aged 45 years or less with detectable serum levels of AMH at baseline had undetectable levels after RT.**

Conclusion: **Preoperative RT was associated with impairment in sexual function in women with rectal cancer. This needs to be considered when discussing choice of treatment and rehabilitation. In younger women, undetectable AMH levels after RT indicate an irreversible loss of ovarian follicles.**

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Introduction

Multimodal treatment for rectal cancer may have a negative impact on sexual function in women owing to treatment- and disease-related effects on physical and psychological health and relationship with partner[1,2]. The surgery can cause anatomical changes, scarring and injury to the autonomous nervous system[3]. Pelvic radiotherapy (RT) induces a pelvic inflammatory response with genital fibrosis, vascular and neurological damage[4,5]. Loss of ovarian function resulting from irradiation or surgical removal may impair sexual function, especially in premenopausal women[6]. In the Dutch total mesorectal excision (TME) trial[7], which used a non-validated scale, RT was associated with an increase in general sexual dysfunction, but not dyspareunia or vaginal dryness. Other proposed risk factors for sexual dysfunction in patients with rectal cancer include type of surgery (abdominoperineal excision (APE) *versus* anterior resection (AR))[1], presence of a stoma[2,7], older age[1,7,8] and psychological factors[9]. To date, few studies have focused on sexual function in women treated for rectal cancer[10,11]. Inclusion and response rates were lower in women than men in studies on sexual function after treatment for colorectal cancer, and several different questionnaires were used to report female sexual function, which complicates interpretation of data and comparisons across studies[10].

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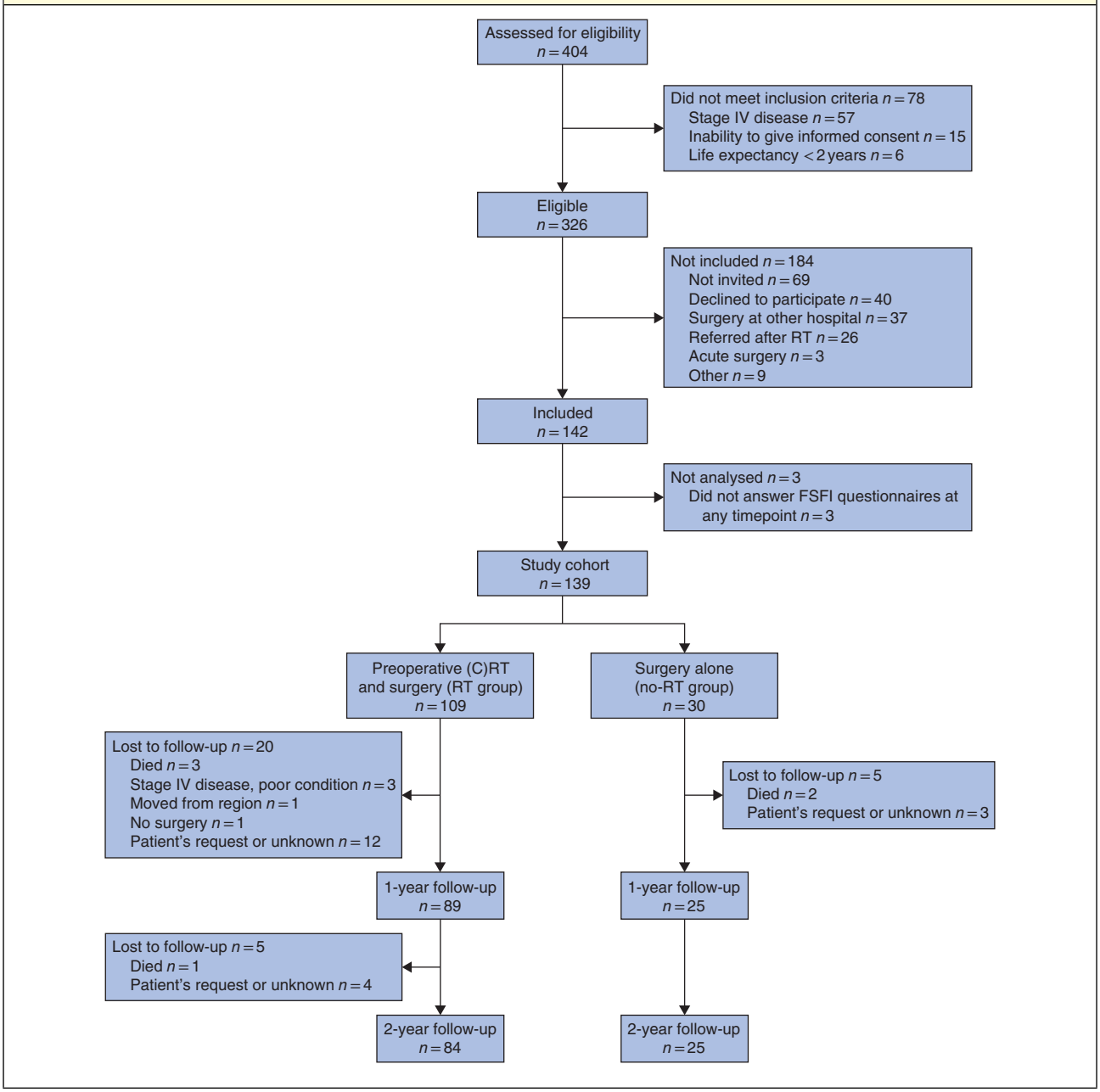
Fig. 1 Study flow chart



(C)RT, (chemo)radiotherapy; FSFI, Female Sexual Function Index.

Anti-Müllerian hormone (AMH), produced by the granulosa cells of immature ovarian follicles, has a role in the regulation of ovulation[12]. Serum levels of AMH can be used as a measure of ovarian reserve in women of reproductive age. Reduced levels are seen after gonadotoxic cancer treatment, but information is lacking regarding AMH levels after RT for rectal cancer[13].

The aim of this prospective longitudinal cohort study was to investigate the impact of RT on sexual and ovarian function in women treated for rectal cancer.

Methods

Details of this longitudinal cohort study have been described previously[14]. Women with stage I–III rectal

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Table 1 Patient, tumour and treatment-related characteristics for the study cohort

	Preoperative RT ($n = 109$)	No preoperative RT ($n = 30$)	*P*#
Age (years)*	62 (26–81)	69 (46–90)	0·002**
BMI (kg/m²)*	24·2 (17·3–37·4)	24·4 (18·2–39·5)	0·849**
ASA fitness grade			0·145
I	35	7	
II	58	13	
III	16	9	
Tumour distance from anal verge (cm)		1	0·130
0–4	45	4	
5–10	40	14	
11–15	23	12	
Type of preoperative RT	1		
Short course (5 Gy × 5)	72	_	
Long course (2 Gy × 25 or 1·8 Gy × 28)	37	_	
Type of surgery			
Anterior resection	54	20	0·056
Abdominoperineal excision†	53	8	
No abdominal surgery	2	2	
Resection of gynaecological organs‡			
Hysterectomy	13	5	0·531
Unilateral/bilateral oophorectomy	16	4	1·000
Partial vaginal resection	9	0	0·205
pTNM stage			0·789
0	10	1	
I	24	8	
II	29	6	
III	39	13	
IV§	4	1	
Neoadjuvant chemotherapy¶	35	1	0·001
Adjuvant chemotherapy	36	9	0·827

*Values are median (range). †Including one Hartmann's procedure in each group. ‡Numbers include resections before study inclusion and as part of rectal cancer surgery; before inclusion, seven and six patients in the radiotherapy (RT) and no-RT groups respectively had undergone hysterectomy, five and one had undergone unilateral oophorectomy, and seven and three had undergone bilateral oophorectomy; no patient had undergone vaginal resection. §Distant metastases shortly after inclusion. ¶Standard chemoradiotherapy or neoadjuvant combination chemotherapy before RT. #Fisher's exact test, except **Wilcoxon rank-sum test.

cancer were included prospectively between June 2008 and August 2013 from five Swedish referral centres for rectal cancer surgery (Karolinska University Hospital, Ersta Hospital, Örebro University Hospital, Linköping University Hospital and Norrköping Hospital). Follow-up time was 2 years. Questionnaires on sexual function and psychological well-being were collected at baseline, and 1 and 2 years after operation. Venous blood samples were analysed at baseline and 1 year after surgery. In patients treated with RT, an additional blood sample was taken after RT, the day before surgery. The study was approved by the Regional Ethical Review Board in Stockholm (2008/247-31/3, 2012/1730-30/3).

Participants

Women were screened for inclusion at multidisciplinary team conferences, and included at a preoperative outpatient visit irrespective of age and level of sexual activity. Inclusion criteria were: age at least 18 years, stage I–III rectal cancer, and planned abdominal surgery with or without preoperative (chemo)RT. Exclusion criteria were inability to give informed consent and life expectancy less than 2 years.

Preoperative radiotherapy and chemotherapy

Patients were treated with surgery alone (no-RT group) or neoadjuvant (chemo)RT and surgery (RT group).

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Table 2 Female Sexual Function Index total and domain scores, and proportion of women with sexual dysfunction

	Preoperative RT ($n = 109$)			No preoperative RT ($n = 30$)			
	No. of women	FSFI score*	*P* for longitudinal comparison§	No. of women	FSFI score*	*P* for longitudinal comparison§	*P* for cross-sectional comparison#
FSFI total score†							
Baseline	89	18·5 (2·0–36·0)		25	6·7 (2·0–30·7)		0·024
1 year	79	11·1 (2·0–34·5)	0·004	21	5·8 (2·0–33·3)	0·906	0·751
2 years	53	10·8 (2·0–34·8)	< 0·001	12	6·5 (2·3–31·7)	0·327	0·766
Desire							
Baseline	107	2·4 (1·2–6·0)		30	1·8 (1·2–4·2)		0·320
1 year	89	1·8 (1·2–5·4)	0·027	25	1·8 (1·2–4·8)	0·251	0·804
2 years	62	1·2 (1·2–4·8)	0·005	15	1·8 (1·2–3·6)	0·365	0·699
Arousal							
Baseline	105	2·1 (0–6·0)		29	0·9 (0–5·1)		0·142
1 year	89	1·2 (0–5·7)	0·005	25	1·2 (0–5·1)	0·612	0·857
2 years	58	1·2 (0–6·0)	0·002	15	0·9 (0–5·1)	0·098	0·686
Lubrication							
Baseline	105	2·4 (0–6·0)		29	0·3 (0–5·7)		0·093
1 year	88	0·6 (0–6·0)	0·002	25	0 (0–6·0)	0·364	0·695
2 years	57	1·2 (0–6·0)	< 0·001	15	0·3 (0·3–6·0)	0·516	0·856
Orgasm							
Baseline	105	2·0 (0–6·0)		29	0 (2·4–6·0)		0·012
1 year	88	0 (0–6·0)	0·173	25	0 (0–6·0)	0·390	0·569
2 years	57	1·2 (0–6·0)	0·010	15	0 (0–5·6)	0·351	0·601
Satisfaction							
Baseline	90	3·2 (0·8–6·0)		25	3·2 (0·8–6·0)		0·266
1 year	79	3·2 (0·8–6·0)	0·116	21	3·2 (0·8–6·0)	0·599	0·912
2 years	54	2·4 (0·8–6·0)	< 0·001	14	1·8 (0·8–6·0)	0·012	0·450
Pain‡							
Baseline	104	0·4 (0–6·0)		29	0 (0–6·0)		0·010
1 year	87	0 (0–6·0)	0·002	24	0 (0–6·0)	0·344	0·842
2 years	57	0 (0–6·0)	0·002	15	0 (0–6·0)	0·948	0·949
Proportion with sexual dysfunction (FSFI total score ≤ 26·55)							
Baseline	59 of 89			24 of 25			0·002**
1 year	66 of 79		0·008¶	17 of 21		0·500¶	0·751**
2 years	50 of 53		< 0·001¶	13 of 14		1·000¶	1·000**

*Values are median (range). †Scores were calculated only for questionnaires with no missing answers. ‡Low score indicates more pain. RT, radiotherapy; FSFI, Female Sexual Function Index. §Scores at 1 and 2 years *versus* baseline (Wilcoxon's signed-rank test, except ¶McNemar's exact test); #comparison between groups (Wilcoxon's rank-sum test, except **Fisher's exact test).

Preoperative RT was either short course ($5\,\text{Gy} \times 5$) or long course ($2\,\text{Gy} \times 25$ or $1{\cdot}8\,\text{Gy} \times 25 + 3$ fractions of boost), with or without concomitant or sequential chemotherapy[14].

Sexual function

The primary outcome, sexual function, was assessed using the Female Sexual Function Index (FSFI)[15]. The FSFI questionnaire is a 19-item multiple-choice, self-assessment tool, validated for use in the general population[15,16] as well as for patients with cancer[17,18]. It covers six domains of sexual function in women: desire, arousal, lubrication, orgasm, satisfaction and pain. A total FSFI score can be calculated when all items are completed. Fifteen items have the response option 'no sexual activity' or 'did not attempt intercourse', which can be interpreted as meaning that no sexual activity occurred during the previous 4 weeks, or sexual function was impaired to a degree that sexual activity was not possible[17]. A sensitivity analysis was undertaken

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Table 3 Proportions of women in relationship with partner or with follicle-stimulating hormone over 25 units/l, and psychological well-being scores over time

	Preoperative RT ($n = 109$)			No preoperative RT ($n = 30$)			
	Proportion of women*	No. of missing values	*P* for longitudinal comparison§	Proportion of women*	No. of missing values	*P* for longitudinal comparison§	*P* for cross-sectional comparison#
Relationship with partner							
Baseline	77 of 108	1		19 of 30			0·501
1 year	62 of 89		1·000	16 of 25		1·000	0·630
2 years	42 of 64	20	0·063	11 of 15	10	1·000	0·561
PGWBI total score†							
Baseline	72·7 (20·0–95·5)	3		71·8 (35·5–94·5)			0·763**
1 year	72·7 (22·7–97·3)	1	0·765¶	77·3 (59·1–94·5)		0·189¶	0·200**
2 years	75·0 (30·9–99·1)	20	0·880¶	72·7 (25·5 –90·0)	9	0·959¶	0·790**
FSH > 25 units/l‡							
Baseline	89 of 107	2		28 of 30			0·243
Post RT	73 of 83	6	0·508	–	–	–	–
1 year	84 of 87	2	0·002	23 of 24	1	1·000	0·628

*Unless indicated otherwise; †values are median (range). ‡Indicating postmenopausal status. RT, radiotherapy; FSH, follicle-stimulating hormone; PGWBI, Psychological General Well-being Index. §Scores at 1 and 2 years *versus* baseline (McNemar's exact test, except ¶Wilcoxon's signed-rank test); #comparison between groups (Fisher's exact test, except **Wilcoxon's rank-sum test).

that included women who reported sexual activity, defined as absence of the response option 'no sexual activity' or 'did not attempt intercourse' in at least one FSFI domain including items with any of these response options. A total FSFI score of less than 26·55 was used to define overall sexual dysfunction[19]. There is no established minimal clinically important difference[20].

Psychological well-being

Psychological well-being was measured using the Psychological General Well-being Index (PGWBI). The questionnaire includes 22 items covering six domains: anxiety, depressed mood, positive well-being, self-control, general health and vitality. The global PGWBI score, ranging from 0 to 100, was calculated[21].

Labaratory analyses and ovarian function

Follicle-stimulating hormone (FSH) levels were measured by fluorescence immunoassay using an AutoDELFIA® immunoassay system (PerkinElmer, Waltham, Massachusetts, USA). The total coefficient of variation for FSH was 3 per cent at 7·6 units/l, and 4 per cent at both 22 and 38 units/l.

Ovarian reserve was assessed in women aged 45 years or less by the level of AMH, which was measured using a commercially available enzyme-linked immunoassay kit (UltraSensitive AMH/MIS ELISA; AnshLabs, Webster, Texas, USA). AMH levels below 0.07 μg/l were regarded as undetectable as the coefficient of variation for lower values exceeds 20 per cent. The total coefficient of variation was approximately 4·0–4·5 per cent at 1·9 μg/l.

Bias

Use of the FSFI questionnaire in women who are not sexually active results in low scores towards the sexual dysfunction pole[17,22]. In the present study, this may have led to a floor effect, with underestimation of the change in sexual function over time. To avoid information bias, a sensitivity analysis (described above) was performed, which included women who reported sexual activity. The majority of the questionnaires were completed during study visits, and sent a second time if not returned by mail to improve the response rate. At the baseline visit, women were asked to complete questionnaires according to their functional level before the diagnosis of rectal cancer or occurrence of symptoms from the disease.

Statistical analysis

The initial sample size calculation was based on reference FSFI data[19]. A preplanned interim analysis showed that this approach was problematic as a large proportion of the study participants did not report sexual activity[23]. A second sample size calculation based on total mean FSFI score at baseline was performed. A sample size of 99 women (115 if

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Table 4 Results of univariable and multivariable longitudinal regression analyses of change in Female Sexual Function Index total score

	Univariable analysis		Multivariable analysis	
	Mean change in FSFI total score*	*P*	Mean change in FSFI total score*	*P*
Treatment group				
No preoperative RT	Reference		Reference	
Preoperative RT	−9·43 (−16·82, −2·04)	0·012	−9·28 (−16·57, −2·00)	0·013
Age (years)				
≤ 55	Reference		Reference	
56–70	−3·09 (−6·13, −0·04)	0·047	−3·84 (−6·96, −0·72)	0·016
> 70	−10·45 (−14·07, −6·84)	< 0·001	−8·67 (−12·26, −5·07)	< 0·001
BMI (kg/m^2)				
< 25·0	Reference			
25·0–29·9	1·74 (−1·75, 5·24)	0·328		
30·0–40·0	−1·01 (−5·24, 3·07)	0·609		
ASA fitness grade				
I	Reference		Reference	
II	−4·59 (−8·26, −0·93)	0·014	−2·56 (−5·65, 0·52)	0·104
III	−7·59 (−12·59, −2·60)	0·003	−3·24 (−7·02, 0·54)	0·093
Type of preoperative RT				
Short course	Reference			
Long course	0·86 (−3·28, 5·00)	0·683		
Type of surgery				
Anterior resection	Reference			
Abdominoperineal excision	−1·33 (−4·54, 1·88)	0·417		
Adjuvant chemotherapy				
No	Reference			
Yes	2·44 (−1·10, 5·97)	0·177		
Relationship with partner				
Yes	Reference		Reference	
No	−9·40 (−12·40, −6·41)	<0·001	−7·77 (−10·83, −4·71)	< 0·001
PGWBI score	0·13 (0·04, 0·22)	0·004	0·15 (0·08, 0·22)	< 0·001
FSH (units/l)				
≤ 25	Reference			
> 25†	−2·97 (−7·32, 1·39)	0·182		

Values in parentheses are 95 per cent confidence intervals. *The coefficients represent the difference between groups in mean change in Female Sexual Function Index (FSFI) during the study interval (baseline to 2 years after surgery). †Indicates postmenopausal status. RT, radiotherapy; PGWBI, Psychological General Well-being Index; FSH, follicle-stimulating hormone.

correction for non-parametric statistics was applied) would have 80 per cent power to detect a difference in mean total FSFI score of 3·0 (20 per cent) in the total cohort over time, assuming a standard deviation of differences of 10·58, using a paired *t* test with a 0·05 two-sided significance level. When loss to follow-up was accounted for, the estimated required sample size was 140 women.

Wilcoxon's rank-sum and Fisher's exact tests were used for cross-sectional comparison of groups, and Wilcoxon's signed-rank and McNemar's tests for longitudinal analyses. A two-sided 0·05 level of statistical significance was chosen. The longitudinal data analysis was based on general estimating equation (GEE) linear regression with robust standard error. The mean change in FSFI score between baseline and 2 years after surgery was compared among the RT and no-RT groups by linear combination of the interaction terms of RT × study visit. Missing answers in FSFI questionnaires did not follow any pattern, and for this reason imputation of missing answers was considered not applicable.

The following variables were evaluated for potential confounding and effect modification: age (18–55, 56–70, more than 70 years), BMI (less than 25·0, 25·0–29·9, 30·0–40·0 kg/m^2), physical status (ASA grade I–III), relationship with partner (yes, no), total PGWBI score, FSH level (25 units/l or less, over 25 units/l), type of

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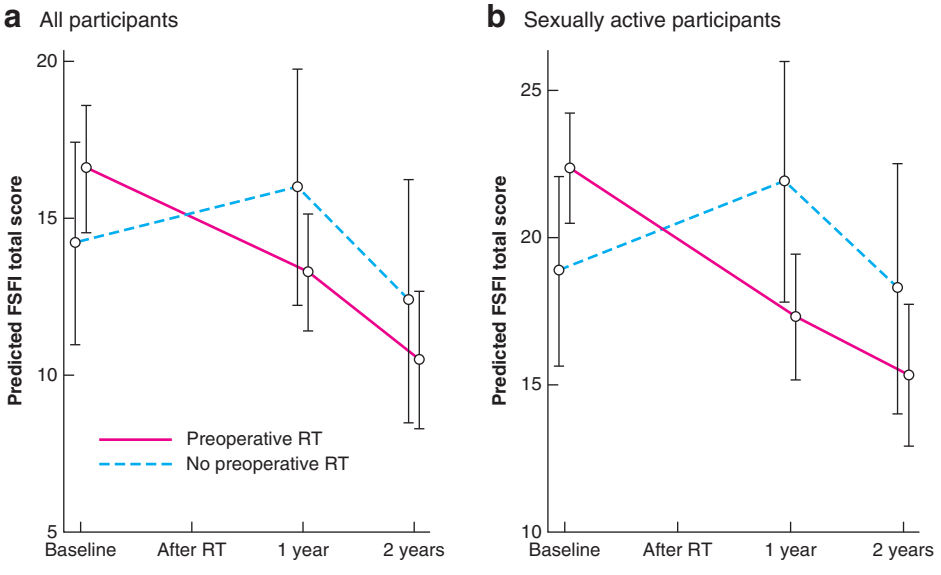
Table 5 Longitudinal regression analysis of change in Female Sexual Function Index total and domain scores

	All participants		Sexually active participants*	
	Mean change in FSFI scores†	*P*	Mean change in FSFI scores†	*P*
FSFI total score				
No preoperative RT	Reference		Reference	
Preoperative RT	−9·33 (−16·66, −1·99)	0·013	−14·53 (−23·85, −5·20)	0·002
Desire				
No preoperative RT	Reference		Reference	
Preoperative RT	−0·48 (−1·27, 0·31)	0·231	−0·99 (−1·88, −0·09)	0·031
Arousal				
No preoperative RT	Reference		Reference	
Preoperative RT	−1·23 (−2·35, −0·10)	0·033	−1·66 (−3·03, −0·28)	0·018
Lubrication				
No preoperative RT	Reference		Reference	
Preoperative RT	−1·93 (−3·59, −0·26)	0·023	−2·17 (−4·43, 0·09)	0·059
Orgasm				
No preoperative RT	Reference		Reference	
Preoperative RT	−1·79 (−3·51, −0·06)	0·042	−2·29 (−4·58, 0·00)	0·050
Satisfaction				
No preoperative RT	Reference		Reference	
Preoperative RT	−0·25 (−1·53, 1·02)	0·696	−1·10 (−2·64, 0·44)	0·160
Pain				
No preoperative RT	Reference		Reference	
Preoperative RT	−2·75 (−4·76, −0·73)	0·008	−3·71 (−6·66, −0·75)	0·014

Values in parentheses are 95 per cent confidence intervals. *Absence of Female Sexual Function Index (FSFI) response option 'no sexual activity' or 'did not attempt intercourse' in at least one FSFI domain including items with any of these response options. †The coefficients represent mean change in FSFI scores for the radiotherapy (RT) compared with the no-radiotherapy (reference) group during the study interval (baseline to 2 years after surgery). Longitudinal regression models were adjusted for age, Psychological General Well-being total score and relationship with partner.

Fig. 2 Predicted Female Sexual Function Index total scores



a All participants, **b** sexually active participants. Values are mean with 95 per cent confidence intervals (error bars). FSFI, Female Sexual Function Index; RT, radiotherapy. **a** $P = 0{\cdot}013$, **b** $P = 0{\cdot}002$ (longitudinal regression model adjusted for age, Psychological General Well-being Index total score and relationship with partner).

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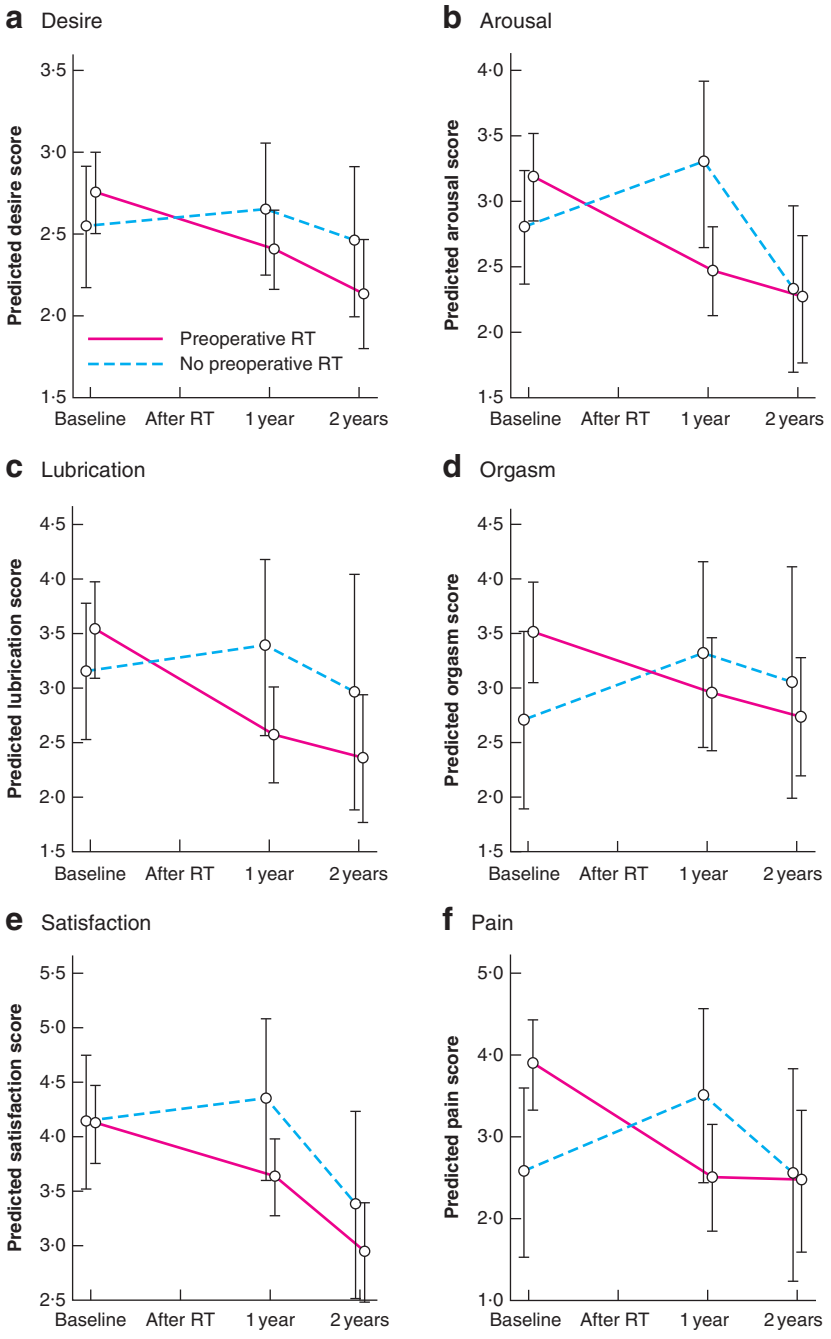
Fig. 3 Predicted Female Sexual Function Index domain scores among sexually active participants



a Desire, **b** arousal, **c** lubrication, **d** orgasm, **e** satisfaction and **f** pain. Values are mean with 95 per cent confidence intervals (error bars). RT, radiotherapy. **a** $P = 0{\cdot}031$, **b** $P = 0{\cdot}018$, **c** $P = 0{\cdot}059$, **d** $P = 0{\cdot}050$, **e** $P = 0{\cdot}160$, **f** $P = 0{\cdot}014$ (longitudinal regression model adjusted for age, Psychological General Well-being Index total score and relationship with partner).

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RT (short course, long course), adjuvant chemotherapy (yes, no) and type of surgery (APE, AR). The variables were included in the final GEE model if they changed point estimates by more than 10 per cent or were significant effect modifiers in the univariable and multivariable analyses.

Statistical analyses were performed with Stata® version 14.1 (StataCorp, College Station, Texas, USA).

Results

In total, 326 of 404 women with rectal cancer were eligible for the study (*Fig. 1*). Sixty-nine women were never invited to participate, which was the main reason for not being included. Of 142 patients included, three women were excluded from analysis as they did not answer any of the FSFI items at any of the three time points; 139 women were included in the analysis. Of these, 109 (78·4 per cent) had preoperative RT and 30 (21·6 per cent) did not. Twenty-five participants (22·9 per cent) in the RT group and five in the no-RT group were lost to follow-up during 2 years after surgery.

Women who received preoperative RT were younger than those who did not (median age 62 *versus* 69 years; $P = 0·002$) (*Table 1*). The proportion of APEs was 53 of 107 (49·5 per cent) in the RT group and eight of 28 in the no-RT group ($P = 0·056$). Nine women in the RT group had partial resection of the vagina compared with none in the no-RT group. Thirty-six women who had preoperative RT (33 per cent) and nine who did not were treated with adjuvant chemotherapy ($P = 0·827$).

Sexual function

At baseline, the median FSFI total score was 18·5 (range 2·0–36·0) in the RT group and 6·7 (2·0–30·7) in the no-RT group ($P = 0·024$) (*Table 2*). The median score declined to 10·8 (2·0–34·8) ($P < 0·001$) and 6·5 (2·3–31·7) ($P = 0·327$) respectively during follow-up. Domain scores that differed between treatment groups at baseline were those for orgasm (2·0 (0–6·0) and 0 (2·4–6·0) in the RT and no-RT groups respectively; $P = 0·012$) and pain (0·4 (0–6·0) and 0 (0–6·0) respectively; $P = 0·010$). There were no significant differences between groups at the subsequent measurement points. Over time, there was a statistically significant reduction in all domain scores in the RT group, but only for the satisfaction domain score in the no-RT group.

The proportion of women with sexual dysfunction (FSFI score below 26·55) was 59 of 89 (66 per cent) in the RT group and 24 of 25 in the no-RT group at baseline ($P = 0·002$). This increased to 50 of 53 (94 per cent) in the RT group after 2 years ($P < 0·001$). The PGWBI total score did not vary significantly between groups or over time (*Table 3*), nor did PGWBI domain scores (data not shown). Sixty-three of 89 and 16 of 25 women were sexually active at baseline in the RT and no-RT groups respectively ($P = 0·624$).

Longitudinal regression analysis

In univariable longitudinal regression analysis, RT, age, ASA grade, relationship with partner and PGWBI score were associated with mean change in FSFI total score (*Table 4*). These associations persisted in the multivariable analysis, with the exception of ASA grade.

The mean change in FSFI total score and all domain scores between the RT and no-RT groups, adjusted for age, PGWBI total score and partner relationship is shown in *Table 5*, *Figs 2* and *3*. The adjusted mean decline in FSFI total score was −9·33 (95 per cent c.i. −16·66 to −1·99; $P = 0·013$) for preoperative RT compared with no preoperative RT by 2 years after surgery. RT was associated with a significant decrease over time in the total FSFI scores, and domain scores for arousal, lubrication, orgasm and pain. The decrease in desire and satisfaction scores was

Table 6 Anti-Müllerian hormone levels in premenopausal women

		No. of ovaries		Anti-Müllerian hormone (μg/l)*		
Age (years)	RT (Gy)	Baseline	1 year after surgery	Baseline	After RT, before surgery	1 year after surgery
38	25	2	2	4·30	–*	–*
26	25	2	2	2·50	0·19	Not detectable
35	50·4	2	2	1·20	Not detectable	Not detectable
40	50·4	2	2	1·20	Not detectable	Not detectable
39	25	2	2	0·20	Not detectable	Not detectable
44	50·4	2	0	0·18	Not detectable	Not detectable†

*Not lost to follow-up but did not participate in blood sampling after radiotherapy (RT) or 1 year after surgery. †Patient had bilateral oophorectomy during surgery for rectal cancer.

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not statistically significant. In sexually active women, the adjusted mean decline in FSFI total score was −14·53 (95 per cent c.i. − 23·85 to −5·20; $P = 0·002$) for RT compared with no RT.

Anti-Müllerian hormone analysis in premenopausal women

Six of nine premenopausal women age 45 years or younger, all treated with RT, had baseline serum levels of AMH above the detection limit (*Table 6*). The AMH levels decreased after RT, and 1 year after surgery all five women with available AMH follow-up had levels below the detection limit.

Discussion

The addition of preoperative RT to surgery in sexually active women treated for rectal cancer was associated with an adjusted mean decline in total FSFI score of −14·53 by 2 years after surgery in this prospective longitudinal cohort study. None of six premenopausal women with RT had detectable AMH levels 1 year after operation.

The FSFI was used to measure sexual function in the present study, as suggested by the Patient-Reported Outcomes Measurement Information System Sexual Function Committee[18] as well as the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology[24]. Baseline FSFI scores of the total cohort were comparable with scores from earlier studies on women with colorectal cancer and other malignancies[11,18], and well below the established cut-off score of less than 26·55 for sexual dysfunction. This may be explained by the cut-off being defined in the context of sexually active, younger women[19]. Interest in sexual activity and sexual function have been related negatively to age in other studies[25,26]. The high proportion of sexual dysfunction at baseline in the present study is therefore not surprising. The present results indicate an association between RT and a decline in all measured aspects of sexual function but desire (sexually active women only) and satisfaction. This is in contrast to the Dutch TME trial[27], which reported an association only between RT and global sexual dysfunction in women, but not between RT and the other domains of sexual function analysed (dyspareunia and vaginal dryness).

Increasing age, absence of relationship with partner and a decrease in PGWBI score were all associated with decreasing FSFI score in the present study. The negative impact of preoperative RT on sexuality could be explained by the fact that normal tissue within the irradiated area is damaged, which in turn may lead to vascular and genital tissue fibrosis, vaginal narrowing and loss of elasticity, pelvic pain and neurological damage[4,5,28]. An additional factor contributing to sexual dysfunction could be RT-induced impairment of ovarian androgen production[14]. Apart from these physical effects, relationship factors are important for sexual function[29]. Being in a relationship may also have an impact on outcome because some of the FSFI items are difficult to answer for individuals without a partner[30]. Psychological well-being can have a negative influence on sexual function and vice versa[31,32]. In the present study, PGWBI scores were comparable with scores in the general population[33] and did not change significantly over time. This is consistent with earlier studies[34,35] reporting similar or even improved psychological well-being or quality of life after rectal cancer treatment compared with the general population.

The undetectable AMH levels seen after RT indicate a permanent loss of fertility in premenopausal women. This is consistent with earlier studies reporting on women treated for gynaecological malignancies[36], and expected biologically as RT with a dose of less than 2 Gy leads to cell death in half of oocytes[37]. Younger women should be offered the possibility of discussing fertility before starting treatment. Cryopreservation of ovarian tissue or ovarian transposition to spare the ovaries from irradiation may be of interest.

Inclusion in the present study was not restricted by age or sexual activity. Eligible women who were not included had a similar clinical tumour stage but were older and had more co-morbidity[23]. RT was given according to the recommendation of the multidisciplinary team conference, resulting in baseline differences in type of surgery and frequency of neoadjuvant chemotherapy. The proportion of patients with a partner, PGWBI score and menopausal status did not differ between the treatment groups at baseline, which implies that the baseline difference in FSFI was related to age. Sexual inactivity may lead to differential misclassification of outcome (FSFI scores) owing to difficulties in interpretation of data when the FSFI is used in sexually inactive women[17]. Nevertheless, results of the sensitivity analysis that included sexually active participants only were consistent with those for all participants. The potential recall bias at baseline, possibly introduced by asking participants to answer questionnaires according to their sexual function before diagnosis or symptoms of disease, was non-differential and the prospective study design minimized recall bias during follow-up. Final longitudinal regression models were adjusted for the confounding effect of age, PGWBI score and relationship with partner. Potential bias from side-effects specific to AR and APE, such as low anterior resection syndrome or permanent stoma, were

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assumed to be covered by the univariable analysis including type of surgery.

The high proportion of patients treated with RT and APE in the present study reflects the fact that the study centres included referral centres for patients with locally advanced rectal cancer. This may reduce the external validity of the results and should be taken into account when they are applied to the total population of women with rectal cancer.

Adding preoperative RT to surgery for rectal cancer seems to be associated with a decline in most aspects of female sexual function measured using the FSFI. This should be considered when deciding on treatment and rehabilitation. The FSFI appears suboptimal for assessing sexual function in women treated for rectal cancer because the advanced age of the patients and sexual inactivity result in low scores, with a potential floor effect reducing the sensitivity for detection of deterioration in a longitudinal study. In premenopausal women, preoperative RT resulted in undetectable levels of AMH, indicating irreversible loss of ovarian follicles and iatrogenic infertility.

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