Acta Oncologica, 2010; 49: 826–832

informa
healthcare

ORIGINAL ARTICLE

Sexual function in females after radiotherapy for rectal cancer

KJERSTI BRUHEIM[1], KJELL MAGNE TVEIT [1,2], EVA SKOVLUND[3], LISE BALTESKARD[4,5], ERIK CARLSEN[6], SOPHIE D. FOSSÅ[2,7] & MARIANNE G. GUREN[1]

[1]*The Cancer Centre, Oslo University Hospital, Ullevål, Oslo, Norway,* [2]*Faculty of Medicine, University of Oslo, Oslo, Norway,* [3]*School of Pharmacy, University of Oslo, Oslo, Norway,* [4]*Department of Oncology, University Hospital of Northern Norway, Tromsø, Norway,* [5]*Norwegian Gastrointestinal Cancer Group,* [6]*Department of Gastrointestinal Surgery, Oslo University Hospital, Ullevål, Oslo, Norway and* [7]*Department of Clinical Cancer Research, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway*

Abstract

Background. Knowledge about female sexual problems after pre- or postoperative (chemo-)radiotherapy and radical resection of rectal cancer is limited. The aim of this study was to compare self-rated sexual functioning in women treated with or without radiotherapy (RT+ vs. RT−), at least two years after surgery for rectal cancer. *Methods and materials.* Female patients diagnosed from 1993 to 2003 were identified from a national database, the Norwegian Rectal Cancer Registry. Eligible patients were without recurrence or metastases at the time of the study. The Sexual function and Vaginal Changes Questionnaire (SVQ) was used to measure sexual functioning. *Results.* Questionnaires were returned from 172 of 332 invited and eligible women (52%). The mean age was 65 years (range 42–79) and the time since surgery for rectal cancer was 4.5 years (range 2.6–12.4). Sexual interest was not significantly impaired in RT+ (n=62) compared to RT− (n=110) women. RT+ women reported more vaginal problems in terms of vaginal dryness (50% vs. 24%), dyspareunia (35% vs. 11%) and reduced vaginal dimension (35% vs. 6%) compared with RT− patients; however, they did not have significantly more worries about their sex life. *Conclusion.* An increased risk of dyspareunia and vaginal dryness was observed in women following surgery combined with (chemo-)radiotherapy compared with women treated with surgery alone. Further research is required to determine the effect of adjuvant therapy on female sexual function.

Rectal excision is associated with a risk of sexual dysfunction due to pelvic autonomic nerve damage, tissue trauma, and scarring [1–4]. Pre- or postoperative (chemo-)radiotherapy (RT) is part of the multimodality treatment of rectal cancer. Preoperative RT reduces the frequency of local recurrence after total mesorectal excision (TME) compared to surgery alone [5,6].

Pelvic radiotherapy may cause adverse effects in normal tissue [7]. Clinical studies have shown that patients treated with radiotherapy for cervical cancer have an increased risk of vaginal problems and sexual dysfunction [8–10]. Furthermore, it has recently been shown that patient-reported symptoms are often underestimated by physicians [11].

Few studies have assessed the effect of RT on sexual function in female rectal cancer patients. In the Dutch TME study, it was observed that preoperative short-term RT (5 Gy × 5) had a negative impact on sexual activity and sexual function [12,13]. An American study suggested that female rectal cancer patients treated with radiotherapy had a four-fold increase in dyspareunia compared to surgery-only patients [14]. With exception of intercourse frequency, binary (yes/no) outcomes were recorded. The response rate for questions about sexual function was 40–50%. Both these studies used non-validated questionnaires for sexual function.

The purpose of the present cross-sectional study was to compare self-rated sexual function in female patients, who had undergone surgery for rectal cancer, and had received (RT+) or not received (RT-) adjuvant radiotherapy. We used a validated questionnaire which assessed sexual side effects, that was designed for female cancer patients that had been treated with pelvic radiotherapy. Our hypothesis

Correspondence: Kjersti Bruheim, The Cancer Centre, Oslo University Hospital, Ullevål, 0407 Oslo, Norway. Tel: +47 23026600. Fax: +47 23026601. E-mail: Kjersti.bruheim@medisin.uio.no

(Received 5 July 2009; accepted 12 April 2010)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/0284186X.2010.486411

was that RT+ patients, compared to RT- patients, had significantly impaired sexual function, and more vaginal problems in terms of dryness, dyspareunia, and reduced vaginal dimension.

Material and methods

Patients were identified from a national database, the Norwegian Rectal Cancer Registry (NRCR), which is part of the Cancer Registry of Norway, and includes all patients with rectal cancer in Norway diagnosed since November 1993. The NRCR contains data on tumor characteristics, the primary treatment, and consecutive information about recurrences and metastases from all hospitals in Norway treating rectal cancer, as well as dates of death.

Study design

The data were collected as part of a national study of late side effects after RT for rectal cancer. We identified all surviving female patients, who had been diagnosed with primary rectal cancer from November 1993 to December 2003 in the NRCR, and who had been treated with pre- or postoperative (chemo-) RT with curative intention (n=170) and were without local recurrence or distant metastases. To serve as controls for the irradiated (RT+) patients, female patients treated with surgery alone (RT-) in the same time period, were sampled from the NRCR (n=370). According to Norwegian guidelines adjuvant (chemo-) radiotherapy is indicated for all T4 tumours, if preoperative MRI reveals a tumor close to the mesorectal fascia (≤3 mm), in non-radically resected tumours or after perioperative perforation of the tumour. Even though the selection criteria for RT implies differences between the two treatment groups, the controls were drawn randomly and were not matched for age, treatment- or disease-related factors, in order to allow analyses of the effects of these variables. Potential confounding factors were adjusted for in multivariable statistical analyses when possible. The identified patients were eligible for the study if they had been treated with a major resection (low anterior resection, abdominoperineal resection, or Hartmann's procedure), had at least two years of follow-up since surgery and were without recurrence or metastases.

All patients were invited by mail to participate in the study. Two reminders were sent to non-responders after approximately two and four weeks. Patients, who returned an informed consent, were thereafter asked to complete the Sexual function and Vaginal Changes Questionnaire (SVQ) and to participate in a telephone interview.

Patients were excluded from the analyses if the telephone interview disclosed that they had developed local recurrence or distant metastases at the time of the study, or if they had received pelvic RT for other malignancies (e.g. uterus or cervix cancer).

Our study was part of a national study assessing late effects from RT for rectal cancer without an upper age limit. However, in the analysis of sexual function, only women younger than 80 years were included, because we anticipated that very few women beyond this age are sexually active.

Sexual functioning

The SVQ is a 17-item questionnaire designed and previously validated to assess sexual function and vaginal changes in patients with gynaecological cancer [15]. The Danish version of the SVQ was obtained from the author of the original validation study and a forward-backward translation was performed. The interpretation of the final version was pilot tested in ten female patients with rectal cancer undergoing treatment at our department. The questions were considered to be relevant also for women treated for rectal cancer, although the SVQ has not been validated for this patient group.

The questionnaire consists of two parts; the first part is answered by all respondents and concerns intimacy, sexual interest, sexual satisfaction and worries about sex-life. The second part is completed only by women who have been sexually active during the last month. This part includes a symptom scale on vaginal changes (VC) comprised of the sum of two questions about lack of lubrication and two on dyspareunia (Table I). Furthermore, there is one question about reduced vaginal dimension, and two about bleeding during intercourse. Finally, there is a sum score of sexual functioning (SF) comprised of the ability to complete intercourse, orgasm, and relaxation after sexual activity. The responses are scored into four categories ("not at all", "a little", "quite a bit", and "very much") that are transformed into a 1–4 scale. In the original questionnaire

Table I. Questions concerning vaginal problems in the SVQ.

11.	Did you feel that your vagina was dry during intercourse?
11a.	If yes, has it bothered you?
12.	Have you had any pain during intercourse?
12a.	If yes, has it bothered you?
13.	Have you experienced bleeding during intercourse?
13a.	If yes, has it bothered you?
14.	Did you feel that intercourse was bothersome because your vagina felt too small?

Answering categories:

Not at all	A little	Quite a bit	Very much
1	2	3	4

questions about ability to complete intercourse and orgasm were scored into the categories "never", "occasionally"," often", "always", but these questions were inadvertently scored into the categories "not at all", "a little", "quite a bit", and "very much". For the multivariable analyses the responses were dichotomized into "quite a bit/very much" or "not at all/ a little". Two questions (about satisfaction/dissatisfaction with sex life and appearance) are scored on a Likert scale ranging 1–7. A higher score on a symptom scale or question represents more symptoms, and a higher score on a function scale represents better functioning. The time frame of the SVQ is the last month.

Telephone interview data

Information about current medication, working status, concomitant disease (diabetes and hypertension), smoking, and presence of stoma was obtained in a structured telephone interview performed by a research nurse or a physician (first author).

Radiotherapy

The standard preoperative and postoperative radiotherapy consisted of 23–25 daily fractions of 2 Gy given in five weeks. The pelvic RT was delivered with a three- or four-field technique or two-field technique, and 6–18 MV photon beams. In most of the period, the RT treatment planning was based on two-dimensional simulation, usually with three standard fields; the cranial field border at the L5-S1 interspace, the lower border close below the anal verge or 3 cm above for more proximal tumours, and the lateral border close to the linea terminalis. An increasing proportion of the patients irradiated after the year 2000 had CT-based 3D treatment planning. In most cases, chemotherapy consisted of bolus 5-fluorouracil (5-FU) and leucovorin according to the Nordic regimen [16,17]. Information on RT dose, number of fields, treatment time, patient positioning, and concomitant chemotherapy was obtained from hospital charts.

Statistics

Data were analyzed with SPSS version 16.0 (SPSS Inc, Chicago, IL). Mann Whitney *U*-test was used to compare groups with continuous variables. Pearson χ^2 test was used for categorical data.

If at least half of the items from the scale had been answered, the missing item was assumed to have values equal to the average of those items which was present. Based on the recommendations from the European Organization for Research and Treatment of Cancer quality-of-life core questionnaire (QLQ C-30), the total scale score was considered to be missing if less than half of the items from the scale had been answered [18].

Logistic regression analyses were performed to adjust for potentially confounding factors. For these analyses the responses to the question about sexual interest and the second part of the questionnaire (answered by sexually active women only) were dichotomized into "quite a bit/very much" or "not at all/a little". The dichotomized scores were used as dependent variables, and RT, age, and stoma as independent variables. All tests were two-tailed, and a p-value <0.05 was considered as statistically significant.

Ethics

The study was approved by the Regional Committee for Medical Research Ethics, of South Eastern Norway.

Results

Patients and treatment

A total of 540 females with primary rectal cancer were identified from the NRCR. Of these, 208 were non-eligible (37 local surgery, 11 deceased or not able to give informed consent, five recurrence or pelvic RT for another malignancy and 155 age $\geq$80 years); thus 332 women were eligible. Of these, 172 women (52%) returned completed questionnaires; 62/118 RT+ (53%) and 110/214 RT− (51%). However, not all questions were answered by all responders.

Responders and non-responders did not differ with respect to type of surgery, T-category, or time since surgery; however, responding patients were younger (median 65 vs. 73 years, $p<0.001$).

Among the responders, 45 patients in the RT+ group (74%) and 73 (69%) in the RT- group had a partner ($p=0.5$). Among the 118 women with a partner, the median age was 62 years among those who were sexually active (n=56), and 67 years among those who were not (n=62). RT+ patients had a shorter median interval since surgery than RT− patients. As a consequence of the selection-criteria for RT, a higher proportion of RT+ patients had pT4 tumours, tumours closer to the anal verge, had undergone abdominoperineal resection and had a stoma compared to RT− patients (Table II). In 19 of the RT+ patients (31%) and 15 of the RT− (14%), the resection included the vagina or internal genitals. TME was performed in 96% of all patients.

Table II. Patient characteristics of responding patients.

	RT+ group n=62	RT− group n=110
Age, median years, (range)	65 (42–79)	66 (50–79)
Time since surgery, median years (range)	4.3 (2.6–10.4)	4.7 (3.0–12.4)
Resection type, n (%)		
Low anterior resection	30 (48)	93 (85)
Abdominoperineal resection	27 (44)	16 (14)
Hartmann's procedure	5 (8)	1 (1)
Stoma present, n (%)	35 (57)	24 (22)
Tumor distance from anal verge, median cm (range)	7 (0–18)	10 (0–19)
(y)pT-stage, n (%)		
T0/T1	6 (10)	16 (15)
T2	8 (13)	37 (34)
T3	42 (67)	53 (48)
T4	6 (10)	4 (3)
Chemotherapy, n (%)	39 (63)	2 (2)

RT was given preoperatively in 33 patients (53%) and postoperatively in 29 patients (47%). The mean dose to the gross tumor volume was 50 Gy (range 34–60). Most patients (97%) were treated with ≥3 fields, 44% in supine and 56% in prone position. Concomitant chemotherapy was given to 39 of the 62 RT+ patients (63%); all had 5 FU based chemotherapy, and in three patients oxaliplatin was also given. Chemotherapy was given to 18 of the 33 patients (55%) who received preoperative radiotherapy, and to 21 of the 29 patients (72%) who received postoperative radiotherapy. Only two RT− patients had received chemotherapy.

The self-reported prevalence of diabetes (4%), hypertension (29%), current smokers (22%), or women currently employed (32%), did not differ significantly between the RT+ and RT− groups. Eight RT+ women (13%) and 11 RT− women (10%) reported to use oestrogen replacement therapy or topical oestrogens (p=0.6).

Female sexual function

There was no significant difference in the score for intimacy, sexual interest, or worries about sex life between RT+ and RT− patients (Table III). A total of 56 women had been sexually active the last month, 20 in the RT+ group and 36 in the RT− group, (representing 44% of RT+ and 47% of RT− women with a partner, p=0.9). When comparing patients with or without a present stoma, there were no statistically significant differences in the proportion of patients who reported being sexually active (42% vs. 49%, respectively, p=0.4) or in the score for satisfaction/dissatisfaction with appearance (mean 4.6 vs. 4.9, respectively, p=0.3). Increasing age was significantly associated with less sexual interest and less sexual activity (data not shown).

In sexually active women, the mean score for VC (lack of lubrication during intercourse and dyspareunia), reduced vaginal dimension and vaginal bleeding during intercourse was significantly higher in the RT+ group compared to the RT− group (Table III). However, there was no significant difference in the score for sexual functioning between the two treatment groups. In the RT+ group 50% (10/20) reported vaginal dryness, compared with 24% (8/34) in the RT− group (p=0.046) (Table IV). For reduced vaginal dimension and dyspareunia the relevant figures were 35% (7/20) vs. 6% (2/34) (p<0.01), and 35% (7/20) vs. 11% (4/36), respectively (p=0.03).

In logistic regression analyses with vaginal or orgasmic problems as the dependent variable there was no significant effect of age, genital resection, chemotherapy or stoma in sexually active women (data not shown). However, the odds for lack of lubrication, dyspareunia, and vaginal constriction was increased in RT+ women compared to RT− women, and the effect remained significant when adjusted for age and stoma (Table IV).

Table III. Sexual function and vaginal changes scores in RT+ and RT− patients.

Scales	Range	n (RT+/RT−)	RT+group Mean (SD)	RT−group Mean (SD)	p*
Intimacy	2–8	(58/102)	5.0 (1.7)	5.03 (1.5)	0.7
Sexual interest	1–4	(59/102)	1.8 (0.8)	1.8 (0.9)	0.8
Worries about sex life	2–11	(55/95)	5.3 (3.0)	4.8 (2.4)	0.6
Vaginal changes**	4–16	(20/35)	9.1 (3.8)	6.8 (3.0)	**0.02**
Vaginal bleeding during intercourse	2–8	(20/34)	2.9 (2)	2.1 (2)	**0.001**
Reduced vaginal dimension	1–4	(20/34)	2.1 (1.2)	1.2 (0.7)	**0.001**
Sexual functioning***	3–12	(19/30)	8.4 (2.1)	9.2 (2.7)	0.15

*Mann-Whitney U test.
**Lack of lubrication, dyspareunia, distress from lack of lubrication/dyspareunia.
***Ability to complete intercourse, orgasm, relaxation after sex.

Table IV. Odds ratio (OR) of sexual dysfunction and vaginal problems in RT+ patients compared to RT− patients, adjusted for age and the presence of stoma.

	RT+	RT−	OR	p	CI
Sexual interest (1)	44/15	78/24	1.2	0.5	0.5–2.8
Lack of lubrication (2)	10/10	8/26	3.5	0.04	1.03–12.1
Dyspareunia (2)	7/13	4/32	4.5	0.04	1.1–18.6
Reduced vaginal dimension (2)	7/13	2/32	8.9	0.01	1.6–50.3
Able to complete intercourse (3)	7/11	5/21	2.3	0.26	0.5–9.5
Reach orgasm (3)	9/10	9/23	2.5	0.1	0.7–8.8

1 = no- low/ quite a bit- very much, 2 = quite a bit- very much/ not at all- a little, 3 = not at all- a little/ quite a bit- very much.

Discussion

The present study indicates that women treated for rectal cancer with pre- or postoperative (chemo-) RT and surgery have significantly more vaginal problems at long time follow-up than women treated with surgery alone. On the other hand, sexual interest and orgasmic function were not significantly impaired in RT+ compared to RT− women and RT+ women did not have significantly more worries about their sex life than RT− women. To our knowledge this is the first study that assesses female sexual function in patients with rectal cancer in long-term follow-up after RT with 50 Gy with a comprehensive questionnaire.

There is increasing awareness about the late side effects of RT for rectal cancer [19]. The most frequent adverse effect is bowel- and anorectal dysfunction (loose stools, evacuation problems and faecal incontinence) [20–23]. In males, pelvic RT is associated with increased risk of erectile dysfunction, lack of ejaculation and decreased libido [24,25]. Fibrosis, with nerve demyelisation and vascular injury are possible mechanisms [26]. There may be several reasons why women experience sexual problems after pelvic RT. Radiotherapy for rectal cancer includes a major part of the internal genitals which may lead to atrophy, fibrosis, adhesions, and shortening of the vagina [7]. Furthermore, the radiation field involves the ovaries. Radiation to the ovaries may cause permanent menopause after a total exposure of 4–7 Gy in women from about 40 years and older [27]. The majority of the women diagnosed with rectal cancer have already reached the age of menopause. In premenopausal women however, radiation-induced ovarian failure may contribute to vaginal dryness and dyspareunia [28].

Sexual function has been investigated in women treated with radiotherapy for cervical cancer [29]. A prospective study by Jensen et al. observed persistent sexual dysfunction and adverse vaginal changes two years after radiotherapy for cervical cancer [9]. Also, Frumovitz et al. found that women treated with radiotherapy had more sexual dysfunction and vaginal problems five years after treatment for cervical cancer, than did those treated with radical hysterectomy and lymph node dissection [10]. On the other hand, Bergmark et al. concluded that radiotherapy, compared to surgery alone had little, if any effect on the prevalence of vaginal shortness, inelasticity, or lubrication in a population of early stage cervical cancer treated with surgery and intracavitary radiotherapy and/or external radiotherapy [30].

Radiotherapy for gynaecological and rectal cancer has similarities, and research results from patients with cervical cancer patients may to some extent be extrapolated to patients with rectal cancer. However, women with cervical cancer are likely to experience more symptoms as they are younger, and a larger proportion is premenopausal compared to women with rectal cancer. Furthermore, it may be more difficult to separate the sexual late effects on genital organs from surgery and those from RT in patients with gynaecological cancer.

Several studies on rectal cancer patients show that sexual function deteriorates after surgery [1,3]. However, the effect of pelvic radiotherapy on female sexual function has been only briefly assessed in subgroup-analyses [3,31–33]. To our knowledge only one large, randomized trial has assessed sexual function in women after RT for rectal cancer [13]. The authors found that preoperative RT (5 Gy × 5) was associated with an increase in sexual dysfunction, similar to the results in the present study. The authors found no increase in vaginal dryness or dyspareunia following RT, but a decrease in sexual interest, pleasure and satisfaction [13]. The data were collected prospectively 3 to 24 months after radiotherapy, while the present results are based on a questionnaire completed 31 to 125 months after initial treatment. The time since radiotherapy may influence the results, as late radiation effects are known to be cumulative with time and may have long latency times.

In the current study, the selection criteria for RT implies differences in tumor and treatment characteristics between RT+ and RT− patients. More RT+ patients had locally advanced tumours and tumours closer to the anal verge, and a higher proportion had abdominoperineal resection with a stoma, resection including the internal genitals or had adjuvant chemotherapy. We aimed to adjust for these factors in multiple regression analysis; however, the low number of sexually active women reduced the possibility to adjust for the desired number of potential confounders. The results should therefore be interpreted with caution. Only about one third of the women had been sexually active the last four

weeks, which is not unexpected in this elderly population. We also found that increasing age was associated with less sexual interest and less sexual activity. Others have found that patients who underwent APR were less sexually active, and that having a stoma was associated with sexual dysfunction [12,14]; however, there were no significant difference in sexual activity between women with or without a stoma in our study.

Like in many other studies of this intimate subject, the study had a fairly low response rate [1,10,34] which may lead to selection bias. The responding women were younger than the non-responding, which most probably have resulted in a selection of more sexually active women. Another limitation to the present study is that the SVQ assesses sexual function mainly by investigating vaginal symptoms and in sexually active women only. Therefore, sexual dysfunction in women without a partner is not evaluated. This may lead to underreporting, as women who are not sexually active may also have vaginal symptoms. Finally, the SVQ was designed and validated for women with gynaecological cancer, and the validity is not necessarily transferable to women with rectal cancer. There was no validated questionnaire for sexual function in rectal cancer patients at the time. However, because we aimed to use a questionnaire that covered vaginal problems often observed after pelvic RT, this questionnaire was considered an appropriate choice.

In modern radiotherapy, CT-based dose planning enables individually formed radiation fields with sparing of normal tissue. However, in our study there has been no effort to spare the female genitals because of the proximity to the CTV. It is not known whether modern radiation techniques like IMRT reduces the radiation-induced genital late effects and this need to be further studied. The feasibility and usefulness of measures like ovarian transposition or vaginal shielding in these patients is not clear, and the impact on sexual function has not been examined. Sexual dysfunction may be aggravated by radiation sensitizing chemotherapy; however, due to the limited number of patients this could not be evaluated in the present study. Future treatment may include combination chemotherapy with for instance irinotecan or oxaliplatin (which may affect peripheral nerves) or antibodies. The late toxicity of this treatment is not known and needs to be addressed in future studies.

Prevention and treatment of the physical late effects from pelvic RT is an important goal for the individual patient with rectal cancer. On a general basis a Cochrane review concludes that there is sufficient evidence of the benefits of vaginal dilators to prevent treatment-induced stenosis after pelvic radiotherapy and that such devices should be recommended [35]. However, the evidence for use of topical estrogens to prevent vaginal bleeding and dyspareunia is less clear and the benefit needs to be confirmed in larger studies [35]. Several non-randomized studies have shown promising results using hyperbaric oxygen in cases of radio necrotic injuries to the perineum and vagina [35]. Finally, consultations with a physician may be beneficial for the diagnosis and treatment of gynaecological side effects following pelvic RT for rectal cancer.

Sexual function and gynaecological problems are intimate subjects that are not easily brought up by all patients or physicians. Providing information about possible side-effects prior to treatment will make it easier for patients to identify and discuss these matters with physicians if symptoms or problems later develop.

Conclusion

An increased risk of dyspareunia and vaginal dryness was observed in women following surgery combined with (chemo-)radiotherapy compared with women treated with surgery alone. Further research is required to determine the effect of adjuvant therapy on female sexual function.

Acknowledgements

This work was supported by a research grant from the Eastern Norway Health Authority and with support from the Norwegian Colorectal Cancer Registry and the Norwegian Cancer Registry. Thanks to the patients who contributed to this study, to Pernille T. Jensen for providing the sexual health questionnaire, and to Mette Wallin and Cathrine Knudsen for their assistance with the data-collection.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Platell CF, Thompson PJ, Makin GB. Sexual health in women following pelvic surgery for rectal cancer. Br J Surg 2004;91:465–8.

[2] Havenga K, Maas CP, DeRuiter MC, Welvaart K, Trimbos JB. Avoiding long-term disturbance to bladder and sexual function in pelvic surgery, particularly with rectal cancer. Semin Surg Oncol 2000;18:235–43.

[3] Hendren SK, O'Connor BI, Liu M, Asano T, Cohen Z, Swallow CJ, et al. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. Ann Surg 2005;242:212–23.

[4] Hendren SK, Swallow CJ, Smith A, Lipa JE, Cohen Z, Macrae HM, et al. Complications and sexual function after vaginectomy for anorectal tumors. Dis Colon Rectum 2007;50:810–6.

[5] Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, et al. The TME trial after a median follow-up of 6 years: Increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007;246:693–701.
[6] Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): A multicentre, randomised trial. Lancet 2009;373:811–20.
[7] Grigsby PW, Russell A, Bruner D, Eifel P, Koh WJ, Spanos W, et al. Late injury of cancer therapy on the female reproductive tract. Int J Radiat Oncol Biol Phys 1995;31: 1281–99.
[8] Schover LR, Fife M, Gershenson DM. Sexual dysfunction and treatment for early stage cervical cancer. Cancer 1989; 63:204–12.
[9] Jensen PT. Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys 2003;56:937–49.
[10] Frumovitz M, Sun CC, Schover LR, Munsell MF, Jhingran A, Wharton JT, et al. Quality of life and sexual functioning in cervical cancer survivors. J Clin Oncol 2005;23:7428–36.
[11] Vistad I, Cvancarova M, Fosså SD, Kristensen GB. Postradiotherapy morbidity in long-term survivors after locally advanced cervical cancer: How well do physicians' assessments agree with those of their patients? Int J Radiat Oncol Biol Phys 2008;71:1335–42.
[12] Lange MM, Marijnen CA, Maas CP, Putter H, Rutten HJ, Stiggelbout AM, et al. Risk factors for sexual dysfunction after rectal cancer treatment. Eur J Cancer 2009;45:1578–88.
[13] Marijnen CA, van de Velde CJH, Putter H, van den BM, Maas CP, Martijn H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: Report of a multicenter randomized trial. J Clin Oncol 2005;23:1847–58.
[14] Tekkis PP, Cornish JA, Remzi FH, Tilney HS, Strong SA, Church JM, et al. Measuring sexual and urinary outcomes in women after rectal cancer excision. Dis Colon Rectum 2009;52:46–54.
[15] Jensen PT. Validation of a questionnaire for self-assessment of sexual function and vaginal changes after gynaecological cancer. Psychooncology 2004;13:577–92.
[16] Brændengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Påhlman L, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 2008; 26:3687–94.
[17] Tveit KM, Guldvog I, Hagen S, Trondsen E, Harbitz T, Nygaard K, et al. Randomized controlled trial of postoperative radiotherapy and short-term time-scheduled 5-fluorouracil against surgery alone in the treatment of Dukes B and C rectal cancer. Norwegian Adjuvant Rectal Cancer Project Group. Br J Surg 1997;84:1130–5.
[18] Fayers PM, Machin D. Quality of life. The assessment, analysis and interpretation of patient-reported outcomes. 2nd ed. Wiley: 2007. pp. 364–8.
[19] Birgisson H, Påhlman L, Gunnarsson U, Glimelius B. Late adverse effects of radiation therapy for rectal cancer—a systematic overview. Acta Oncol 2007;46:504–16.
[20] Peeters KC, van de Velde CJH, Leer JW, Martijn H, Junggeburt JM, Kranenbarg EK, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: Increased bowel dysfunction in irradiated patients—a Dutch colorectal cancer group study. J Clin Oncol 2005;23:6199–206.
[21] Pollack J, Holm T, Cedermark B, Holmstrom B, Mellgren A. Long-term effect of preoperative radiation therapy on anorectal function. Dis Colon Rectum 2006;49:345–52.
[22] Pietrzak L, Bujko K, Nowacki MP, Kepka L, Oledzki J, Rutkowski A, et al. Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: Report of a randomised trial. Radiother Oncol 2007;84:217–25.
[23] Bruheim K, Guren MG, Skovlund E, Hjermstad MJ, Dahl O, Frykholm G, et al. Late side effects and quality of life after radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys 2010;76:1005–11.
[24] Pinkawa M, Gagel B, Piroth MD, Fischedick K, Asadpour B, Kehl M, et al. Erectile dysfunction after external beam radiotherapy for prostate cancer. Eur Urol 2009;55:227–36.
[25] Bruheim K, Guren MG, Dahl AA, Skovlund E, Balteskard L, Carlsen E, et al. Sexual function in males after radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys 2010;76: 1012–7.
[26] van der Wielen GJ, Mulhall JP, Incrocci L. Erectile dysfunction after radiotherapy for prostate cancer and radiation dose to the penile structures: A critical review. Radiother Oncol 2007;84:107–13.
[27] Ogilvy-Stuart AL, Shalet SM. Effect of radiation on the human reproductive system. Environ Health Perspect 1993; 101(Suppl 2):109–16.
[28] Bachmann GA, Leiblum SR. The impact of hormones on menopausal sexuality: A literature review. Menopause 2004; 11:120–30.
[29] Vistad I, Fosså SD, Dahl AA. A critical review of patient-rated quality of life studies of long-term survivors of cervical cancer. Gynecol Oncol 2006;102:563–72.
[30] Bergmark K, vall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. N Engl J Med 1999;340: 1383–9.
[31] da Silva GM, Hull T, Roberts PL, Ruiz DE, Wexner SD, Weiss EG, et al. The effect of colorectal surgery in female sexual function, body image, self-esteem and general health: A prospective study. Ann Surg 2008;248:266–72.
[32] Schmidt CE, Bestmann B, Kuchler T, Kremer B. Factors influencing sexual function in patients with rectal cancer. Int J Impot Res 2005;17:231–8.
[33] Schmidt CE, Bestmann B, Kuchler T, Longo WE, Kremer B. Ten-year historic cohort of quality of life and sexuality in patients with rectal cancer. Dis Colon Rectum 2005;48: 483–92.
[34] Jayne DG, Brown JM, Thorpe H, Walker J, Quirke P, Guillou PJ. Bladder and sexual function following resection for rectal cancer in a randomized clinical trial of laparoscopic versus open technique. Br J Surg 2005;92:1124–32.
[35] Denton AS, Maher EJ. Interventions for the physical aspects of sexual dysfunction in women following pelvic radiotherapy. Cochrane Database Syst Rev 2003;CD003750.