

**LATE SIDE EFFECTS AND QUALITY OF LIFE AFTER RADIOTHERAPY
FOR RECTAL CANCER**

Kjersti Bruheim

The Cancer Centre, Oslo University Hospital, Ullevål, Oslo, Norway

and

Faculty of Medicine, University of Oslo, Oslo, Norway



Colorectal cancerregisteret 



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Abbreviations

APR	abdominoperineal resection
AR	anterior resection
BMI	body mass index
CRT	chemoradiotherapy
CRM	circumferential resection margin
CT	computed tomography
CTV	clinical target volume
EORTC	European Organization for Research and Treatment of Cancer
FSH	follicle-stimulating hormone
5-FU	5-fluorouracil
Gy	gray (absorbed radiation dose)
LENT SOMA	late effects of normal tissue subjective-objective-management-analytical scales
LH	luteinizing hormone
MRI/MR	magnetic resonance imaging
NRCR	Norwegian Rectal Cancer Registry (from January 2007 organized under the Norwegian Gastrointestinal Cancer Group and named the Norwegian Colorectal Cancer Registry)
pT	tumour stage on pathological examination
ypT	tumour stage on pathological examination after preoperative radiotherapy
QLQ-C30	EORTC quality-of-life core questionnaire
QoL	quality of life
RT	radiotherapy
RT+ patients	patients treated with radiotherapy and surgery
RT- patients	patients treated with surgery alone
SHBG	sex hormone-binding globulin
S-testosterone	serum testosterone
TME	total mesorectal excision
TNM	tumour node metastasis (tumour classification system)

List of papers

This thesis is based on the following papers, which are referred to in the text by the Roman numerals I-IV:

Paper I

Bruheim K, Guren MG, Skovlund E, Hjermsstad MJ, Dahl O, Frykholm G, Carlsen E, Tveit KM. Late side effects and quality of life after radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys*, 2009; June 17 (E-pub ahead of print).

Paper II

Bruheim K, Svartberg J, Carlsen E, Dueland S, Haug E, Skovlund E, Tveit KM, Guren MG. Radiotherapy for rectal cancer is associated with reduced serum testosterone and increased FSH and LH. *Int J Radiat Oncol Biol Phys*, 2008; **70**, 722-727.

Paper III

Bruheim K, Guren MG, Dahl AA, Skovlund E, Balteskard L, Carlsen E, Fosså S, Tveit KM. Sexual function in males after radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys*, 2009; Oct 30 (E-pub ahead of print).

Paper IV

Bruheim K, Tveit KM, Skovlund E, Balteskard L, Carlsen E, Fosså SD, Guren MG. Sexual function in females after radiotherapy for rectal cancer. *Submitted*.

1. INTRODUCTION

Incidence and survival of rectal cancer

Colorectal cancer is one of the most common cancers in industrialized countries with an estimated incidence of more than 400 000 new cases annually in Europe (1). In Norway about 3500 new cases were registered in 2007, which makes colorectal cancer the second most common cancer in men and women after prostate and breast cancer (2). Rectal cancer constitutes approximately one-third of all colorectal cancers, and about 5% of all new cases of cancer diagnosed in Norway. Norway reports the highest incidence rate of colorectal cancer among the Scandinavian countries (3). Almost 80% of the patients are aged over 60 years at diagnosis, and the incidence is about 50% higher in men than in women (2).

Key risk factors associated with colorectal cancer are dietary factors (fibre, red meat, fish, calcium. etc.), physical exercise, obesity and alcohol (4-9). Most colorectal cancer cases are sporadic (75-85%) (8). Lynch syndrome and familial adenomatous polyposis (FAP) are well known, but rare, autosomal dominantly inherited conditions (10). Around 5-10% of colorectal cancers are associated with hereditary susceptibility.

The mortality rates from rectal cancer have steadily decreased in Norway as well as in Europe and the USA, in particular over the last decades (11-13). According to the Norwegian Colorectal Cancer Registry, the 5-year survival rate has increased from 25% to over 60% in the period 1965-2007 (Figure 1) (11).

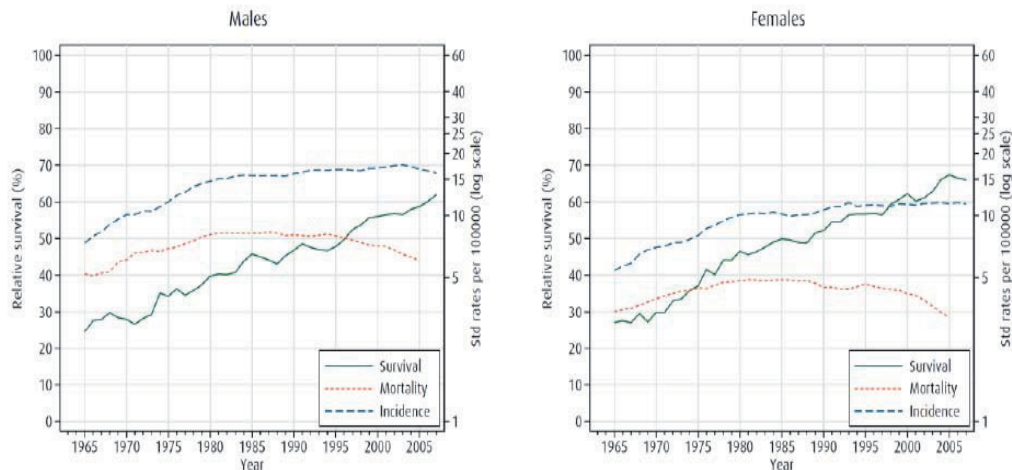


Figure 1. Trends in age standardized relative survival proportions, incidence, and mortality rates (11).

The relative survival shows a pronounced decrease in the first years after diagnosis, but levels off after about 5 years (Figure 2). Patients surviving 6-8 years after diagnosis have a 5-year relative survival probability of >90%, irrespective of age and sex (11). At the end of 2007, there were 9250 people alive who had previously been diagnosed with anorectal cancer in Norway.

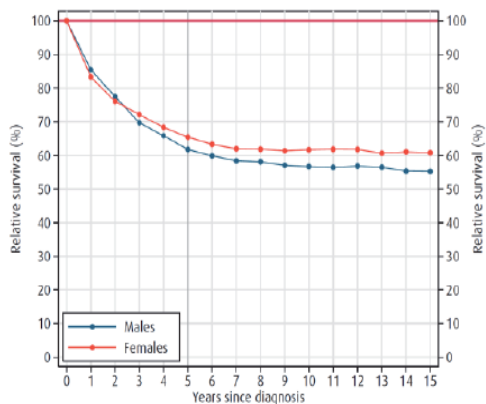


Figure 2. Long-term survival by sex.

Colorectal cancers most often originate in the mucosal glands and are classified as adenocarcinomas. There is no clear anatomical border between the sigmoid colon and the rectum; however, the rectum is usually defined as the bowel below the sacral promontory or within 15-17 cm from the anus, as measured by rigid rectoscopy. In the Norwegian Rectal Cancer Registry (NRCR), tumours up to 20 cm were registered as rectal cancers. Rectal cancers are classified according to the International Union Against Cancer (UICC) staging and the American Joint Commission of Cancer (AJCC) developed TNM classification of malignant tumours (Table I) (14, 15).

Table 1. The UICC staging system and TNM classification

UICC staging system	TNM classification
Stage I	T1-2 N0 M0 T1= tumour invades submucosa T2= tumour invades muscularis propria N0= no regional lymph node metastasis M0= no distant metastasis
Stage II	T3-4 N0 M0 T3= tumour invades through the muscularis propria into the serosa or the perirectal tissues T4= tumour directly invades other organs or structures and /or perforates visceral peritoneum N0= no regional lymph node metastasis M0= no distant metastasis
Stage III	Any T N1-2 M0 N1= metastasis to 1-3 regional lymph nodes N2= metastasis to ≥ 4 regional lymph nodes M0= no distant metastasis
Stage IV	Any T any N M1 M1= distant metastasis

The probability of survival in rectal cancer is closely related to the pathological stage and the resection margins. Whereas patients with stage I disease have a 5-year survival rate of 79%, the survival rate is 64% in patients with stage II and 50% in those with stage III disease according to results from the Norwegian Colorectal Cancer Registry in the years 1993-2004 (16). The circumferential resection margin (CRM) is important because involvement of this margin is associated with an increased risk of local recurrence and decreased survival in rectal cancer patients (17-19).

Clinical staging of the rectal tumour is now performed using magnetic resonance imaging (MRI) and/or endorectal ultrasound (EUS). MRI is highly accurate in predicting CRM positivity, and assessing the depth of extramural spread, particularly in low rectal tumours (8). Preoperative assessment of the distance to the mesorectal fascia plays an important role in decision-making for preoperative (chemo-) radiotherapy, which is primarily given to reduce the risk of local failure. EUS is considered more accurate for assessing the depth of tumour growth into the bowel wall (in T1 and T2 tumours). There is still no reliable imaging technique to evaluate nodal disease preoperatively, because computed tomography (CT), MRI and EUS all rely on size criteria for predicting nodal metastases. The definitive TNM staging and evaluation of the distance to the CRM are performed at the pathological examination of the surgical specimen.

Treatment for rectal cancer

Surgery

Surgery is the mainstay in the treatment of rectal cancer. Over the past few decades, improvement in surgical techniques has led to significantly better prognosis for patients with rectal cancer. This progress started in the 1980s when anatomical dissection, termed "total mesorectal excision" (TME), was developed (20, 21). With TME surgery the surgeon removes the tumour together with the surrounding mesorectal fatty tissue, including lymphatic and venous drainage. More exact surgery and surgery following the embryonic planes has resulted in increased local control with reduced rates of local recurrence and improved survival in rectal cancer (21-23). The TME technique has now become the standard surgical procedure in many countries, and was implemented in Norway during the 1990s.

Although TME is the recommended technique for tumour removal, there are three main surgical procedures for rectal cancer. Anterior resection (AR) is the most widely used technique which re-establishes intestinal continuity and saves the anal sphincter. This operation is recommended when the tumour is situated in the mid- or upper part of the

rectum, or in low cancers, provided that a sufficient distal and circumferential tumour-free margin is attainable. However, in low cancers, where uninvolved resection margins are unattainable with an AR -technique (e.g. if the tumour extends into the pelvic floor), an “abdominoperineal resection” (APR) with amputation of the rectum and a permanent sigmoidostomy is performed. In selected patients, a resection of the rectum with closure of the distal part of the rectum and a permanent sigmoidostomy (the “Hartmann’s procedure”) may be preferred.

The Norwegian Rectal Cancer Project

Before 1993, the procedure for rectal cancer surgery was not standardized in Norway and varied among departments and surgeons. Some Norwegian surgeons had adopted the TME technique with good results (24). However, a national survey, including more than 700 cases, showed a local recurrence rate of 28% after curative rectal cancer resections with traditional surgery (25, 26), which was in sharp contrast to the 5% 5-year local recurrence rate reported after TME in an institution in England (27). On the initiative of dedicated surgeons, the Norwegian Rectal Cancer Project was established in 1993 to improve the surgical technique on a national level, aiming to introduce TME as a national standard for major rectal resections, and to reduce local recurrence rates and improve survival (23). In the first 4 years the proportion of patients undergoing TME increased from 78% to 92% (23). The frequency of 5-year local recurrence rate decreased from 15% in 1994 to 9% in 2004, and the total 5-year survival rate increased from 60% to 69% in the same time period (16).

The Norwegian Rectal Cancer Registry

The Norwegian Rectal Cancer Registry (NRCR) was initiated by the Norwegian Rectal Cancer Project and is a part of the Cancer Registry of Norway, to which all cancers in Norway are reported. The NRCR was established in 1993 and the aim was to establish an instrument for continuous national quality control. Data on tumour characteristics, and primary treatment, and information about recurrences and metastases, are reported prospectively by the surgeons, and follow-up information is obtained by routine reminders sent to surgical departments. The histological assessment of the surgical specimen is extracted from each pathology department’s mandatory reports sent to the Cancer Registry. Information on dates of deaths is transferred from the Statistics Norway.

At the latest update, 10 941 patients with rectal cancer had been registered in the NRCR. The data have been available as quality assurance for hospitals and the results on survival,

recurrence, treatment and diagnostics have been published in national reports as well as in international publications (16). In 2009, the registry expanded to include a national, prospective registration of all patients with colon cancer, and is now named the Norwegian Colorectal Cancer Registry.

Radiotherapy

Historical overview

Before the mid-1980s, patients with rectal cancer usually underwent surgery alone, and the local recurrence rates were between 20 and 30% (25, 26, 28). Trials in the 1980s and 1990s showed a decrease in the risk of locoregional recurrence of approximately 50% with radiotherapy (RT) given preoperatively (25, 29, 30) or chemoradiotherapy (CRT) given postoperatively (26, 31-34), compared with traditional surgery alone. With the substantial decrease in local recurrence after the implementation of TME in the mid-1990s, it was questioned whether RT still had a role in the treatment of resectable rectal cancer (35, 36). However, in 2001 a large randomized Dutch trial observed a significant reduction in local recurrence 2 years after preoperative RT and TME compared with TME alone (37). After 5 years of follow-up, local recurrence rates were significantly better with preoperative RT (6% versus 11%, respectively), but overall survival was not increased (38).

Some countries have a preference for giving RT preoperatively, and others have given CRT postoperatively in primarily resectable tumours. The main advantage of postoperative CRT is that it allows accurate pathological staging and thereby restricts adjuvant treatment to high-risk patients without metastases (39). However, recent randomized controlled trials have shown that preoperative RT is more effective and gives fewer side effects than postoperative CRT (40-42). Furthermore, improvements in preoperative imaging have proven more accurate in identifying patients at risk (43). Nevertheless, the indications for RT are still debated (44).

Another ongoing debate has been on the fractionation schedule in curative RT for high-risk patients (45). Sweden and the Netherlands have developed a schedule with 25 Gy given in five fractions, arguing that "short-course radiotherapy" has a greater dose efficacy, gives less proliferation of subclinical tumour cells, less acute toxicity, better patient compliance and finally is more convenient than a 5-week schedule (46). Furthermore, the Swedish Rectal Cancer Trial has showed improved survival with preoperative RT (30, 47). However, from a radiobiological perspective there has been concern about the late effects with short-course

RT as large fractions are known to increase late morbidity (48). Apart from a Polish study with only 1 year of follow-up, no reports from randomized trials on this subject have so far been published (49). An ongoing study (the Stockholm III study) will address these issues.

RT with "conventional fractionation" of 2 Gy, to a total of 46-50 Gy in 5 weeks, often combined with 5-fluorouracil (5-FU)-based chemotherapy, is currently the standard preoperative treatment for primarily non-resectable cancers in most countries. Several randomized trials and a recent Cochrane review have concluded that preoperative CRT is more effective than preoperative radiotherapy alone, with only a moderate increase in acute toxicity (50-53). Preoperative CRT aims to induce tumour shrinkage and facilitate radical surgery. However, there is no evidence that CRT influences sphincter preservation (54). At present, newer drugs such as irinotecan and oxaliplatin, as well as targeted drugs, are being investigated, but the results on tumour control, survival and toxicity are not conclusive for the time being (55-57).

Radiotherapy Treatment for rectal cancer in Norway

According to Norwegian guidelines, preoperative CRT is recommended when preoperative MRI reveals a distance from tumour (or tumour-infiltrated lymph node) to the mesorectal fascia of ≤ 3 mm, and for all T4 and /or tethered tumours (58). The concomitant chemotherapy may be given as oral treatment with capecitabine 5 days a week during RT treatment, or as bolus 5-FU and folinate according to the Nordic FLv regimen (on days 1, 2, 11, 12, 21, and 22 of RT). Postoperative CRT is indicated in non-radically resected tumours, if CRM < 2 mm, or after perioperative perforation of the tumour or adjacent bowel if treatment was not given preoperatively. In Norway, rectal cancer is usually treated with fractions of 2.0 Gy, 5 days a week for 5 weeks to a total dose of 50 Gy to the gross tumour area and 46 Gy to the area at risk.

Before the late 1990s, the RT treatment was based on two-dimensional simulation of standard fields using bony landmarks: the cranial field border at the L5-S1 interspace, the lower border close below the anal verge or 3 cm above for higher tumours, and the lateral border close to linea terminalis. After the introduction of technical advances in treatment planning around the year 2000, an increasing proportion of patients had CT-based three-dimensional (3D) treatment planning (Figure 3). This may result in improved coverage of the clinical target volume (CTV) and the possibility of avoiding or shielding normal tissue. CT-based treatment planning is now considered mandatory in all RT departments in Norway. The guidelines for delineation of the CTV are based on clinical knowledge of the predominant location of local recurrences and the distribution of lymphatic spread in rectal cancer (58-60).

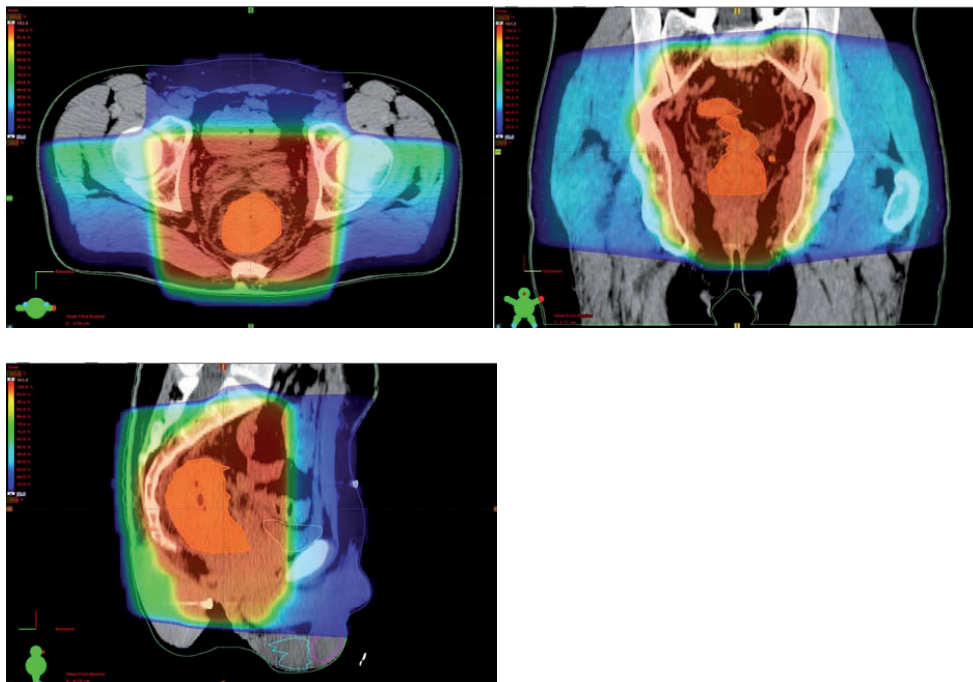


Figure 3. The dose distribution in RT treatment for rectal cancer with one posterior-anterior and two lateral fields.

Along with the improved local control after preoperative RT, and the advances in preoperative MRI, there has been an increase in the use of preoperative RT in Norway; from 8.5% in the years 1998-2001, to 20.2% in 2004, and a decrease in the use of postoperative RT from 13.6% to 3.6% in the same period (16, 61). Today the rate of preoperative RT has reached about 30% (Kjell Magne Tveit, personal communication).

Multidisciplinary team discussions

Advances in MRI has enabled the identification of prognostic factors that are helpful in selecting patients who may benefit from multimodality treatment (43, 62). The national guidelines in Norway have recommended that newly diagnosed patients are discussed in multidisciplinary teams, consisting of specialist surgeons, oncologists, radiologists and pathologists. The aim of the multidisciplinary team discussions has been to select the best

treatment for the patients, and hence to reduce the frequency of local recurrence and improve the survival of rectal cancer patients (63, 64).

Normal tissue side effects from radiotherapy

Therapeutic radiotherapy consists of ionizing radiation, most often electromagnetic radiation, or photons. Ionizing radiation may lead to breaking of chemical bonds, with damage in cellular DNA, either directly or indirectly through free reactive oxygen. The cell then activates a DNA damage response, including several interrelated signalling pathways. The DNA damage sensors recognize DNA damage and may activate three important effect pathways: cell-cycle checkpoints, programmed cell death or DNA repair. In comparison to normal tissue cells, tumour cells have reduced capacity to repair radiation-induced DNA damage (48).

Although radiotherapy primarily affects tissues in the vicinity of the target volume, normal tissue in the beam's path may receive radiation. All tissues will respond to the radiation doses at the molecular, histological or clinical level. However, the probability of developing toxicity depends on several factors: physical factors (e.g. dose, dose per fraction, volume), patient-related factors (e.g. diabetes, hypertension and smoking), genetic factors and other treatment (e.g. prior surgery or concurrent chemotherapy). Hence, not all patients exhibit symptoms or clinical manifestations to the same degree.

Normal tissue effects have been classified according to the time of onset of the clinical symptoms (48). Early (acute) side effects are observed during, or shortly after, radiotherapy. These side effects are usually transient and therefore considered less important for limiting treatment dose. Early effects are seen in tissues with rapid cell proliferation, such as intestinal epithelium, skin and bone marrow. On the other hand, late (chronic) side effects become manifest after a latency of months to many years. They are usually irreversible and often progressive, and appear in tissues with a slower turnover of cells such as subcutaneous tissue, brain, kidney, liver and the intestinal wall. The probability of late tissue morbidity is dose limiting in RT.

In the acute side effects from radiotherapy, the symptoms are based on radiation-induced impairment of cell reproduction (48). The consequence is progressive cell depletion, which is regularly accompanied by inflammatory changes. Late normal tissue effects are based on complex pathophysiological processes that involve radiation-induced changes in parenchymal cells (cell death), fibroblasts (differentiation), vascular endothelial cells (loss of capillaries) and macrophages (48). These cells interact through activation of cytokines and

growth factors, resulting in progressive parenchymal damage, which may lead to loss of function within the irradiated volume. In general, there is little relation between the expression of early and late normal tissue side effects. However, so-called “consequential late effects” may occur when the early reacting tissue compartments (e.g. epithelia) have a protective function against mechanical and/or chemical exposure (65).

Late morbidity after pelvic radiotherapy

Pelvic radiation is used to treat gynaecological, genitourinary and gastrointestinal tumours. Organs at risk in pelvic radiation include the gastrointestinal tract (small bowel, colon, rectum and anus), bone and bone marrow, urinary tract (bladder, urethra and ureter), the sexual organs (vulva, vagina, uterus, ovaries, testicles, prostate gland and penis) and the skin.

The gastrointestinal tract

The small bowel is the organ most often affected by pelvic radiation (66). Gastrointestinal symptoms are more frequent after RT for gynaecological and gastrointestinal cancer compared with RT for urological cancer (67). Symptoms of delayed bowel toxicity usually present after a latency period of between 6 months and 3 years (68). Progressive intestinal wall fibrosis may cause strictures and obstruction, and localized areas with ischaemic necrosis may give rise to fistulas or bowel perforation (68). Radiation-induced chronic diarrhoea is thought to increase proportional to the radiation dose and the irradiated volume (69). Radiation enteropathy of the terminal ileum may be clinically characterized by cobalamin deficiency or subnormal serum-calcium values (70, 71). In patients with severe mucosal injury, chronic ulcers and fibrosis, clinically manifesting as rectal pain, bleeding, tenesmus and faecal urgency, may occur. Histological analyses of the irradiated anal sphincter have revealed time-dependent damage to the myenteric plexus of the internal anal sphincter (72). Clinical studies have suggested that radiation-induced dysfunction of the internal anal sphincter, reduction in rectal compliance and volume and heightened rectal sensitivity may contribute to faecal urgency and incontinence (73, 74).

The most frequent symptoms documented in long-term follow-up of patients treated with RT for rectal cancer are frequent bowel movements, faecal incontinence for loose and solid stools and rectal emptying problems (in about 20-60% of patients) (49, 75-77).

The urinary tract

Late sequelae of the urinary tract include persistent dysuria, contracted bladder, vesicovaginal fistulas and haematuria. Median onset of late urinary side effects is 13-20

months, but latency times can range up to 10 years (48, 78). Morphologically, the initial phase is characterized by progressive mucosal breakdown, ranging from superficial denudation to ulceration (48). The urothelial changes are accompanied by areas of compensatory hyperproliferation and secondary fibrosis of the bladder wall or the urethral sphincters. Telangiectasia can result in severe bleeding episodes.

Radiation effects on the bladder have been described after treatment for among others cervical cancer, prostate cancer and bladder cancer (78-81). However, because the disease itself might have impaired the bladder function, separating radiation effects from the disease may be difficult. In studies of rectal cancer, an increased prevalence of urinary incontinence after RT has been described in some studies (82). However, in a multivariate analysis of more than 700 patients treated with or without preoperative RT and TME, the authors concluded that urinary dysfunction is not related to RT, but rather to surgical nerve damage (83).

Gonads

The testes are normally outside the radiation field, but because of the proximity to the target volume they may receive scattered radiation. It is known that scattered radiation during pelvic RT may affect testicular function, the seminiferous tubules are particularly radiosensitive and total doses of 1.5-2.0 Gy may lead to permanent infertility (84). The effect of radiation on Leydig cell function is less documented; however, there appears to be a dose-response effect (85, 86). Leydig cells account for 75% of the total testosterone production in the normal adult male. Low levels of testosterone may result in decreased libido and sexual dysfunction, increased risk of premature osteoporosis, and changes in body composition and personality (87-89). In a previous study, Dueland et al. measured a mean cumulative dose to the testicles of 8.4 Gy along with a 25% decrease in serum testosterone (S-testosterone) levels 4-6 weeks after RT for rectal cancer (90). Another study found similar results in a group of 11 men (91). At the time of the current study no data after long-term follow-up of patients treated with RT for rectal cancer were available.

Radiation to the ovaries may cause permanent menopause after a total exposure of 4-7 Gy in women aged from about 40 years and older (92). In pelvic RT for rectal cancer, the ovaries are in the radiation field, and in premenopausal women radiation-induced ovarian failure is inevitable.

Sexual function

Pelvic RT can lead to sexual dysfunction in men and women. In men most reports focus on erectile dysfunction, although decreased libido, lack of ejaculation, haemospermia, pain at

orgasm and alteration in the intensity of orgasm have also been described (93-95). The aetiology of erectile dysfunction after pelvic RT is not fully understood, but possible mechanisms include neural injury, vascular alterations and penile corporal structural changes (96). The co-existence of vascular risk factors such as diabetes mellitus, hypertension and smoking may predispose a patient to develop side effects from RT (95, 96).

In men treated with RT for prostate cancer, erectile dysfunction is a well-known sequela and reported in up to 70% of patients (97). In rectal cancer patients, a few studies have reported a higher frequency of erectile dysfunction and ejaculation problems, as well as reduced sexual activity, in patients treated with RT (98-100).

Sexual function in women following RT has been poorly evaluated. Most studies have been conducted in patients with gynaecological cancer, focusing on problems such as vaginal stenosis, dyspareunia, bleeding and lubrication changes (101). Others have also reported lack of sexual interest and dissatisfaction with sex life (102). RT-induced vaginal fibrosis and atrophy may give rise to adhesions and vaginal stenosis, telangiectasia or thinning of the mucosa (94). Serious complications include mucosal necrosis and fistula formation. The data on sexual dysfunction in women treated with RT for rectal cancer are scarce. In one large randomized trial, RT had a negative impact on female sexual activity and sexual function (98, 103); another smaller study found an increased risk of dyspareunia (104). Furthermore, the effect of RT on female sexual function has been only briefly assessed in small subgroup analyses (105-107).

Other late side effects

Preoperative RT significantly increased the risk of venous thromboembolic disease, femoral neck and pelvic fractures in the initial controls of the Stockholm I and II studies (82). However, these findings were not confirmed in the long-term follow-up (108) or in the Dutch TME trial (77). Recently, a prospective American study found a 3-year actuarial rate of sacral insufficiency fractures of 3% after preoperative CRT for rectal cancer (109). About half the patients had symptoms requiring pain medications. An increased risk of cardiovascular disease in the RT group has been observed (108). Furthermore, irradiated patients, 14 years after treatment, have a more than doubled risk of developing second cancers compared with controls treated with surgery only (9.5% vs. 4.3%, respectively) (110).

Health-related quality of life

Health-related quality of life (QoL) is defined as a multidimensional measure, comprising physical, mental and social elements, and symptoms related to the disease and treatment (111). It is considered a subjective measure and is consequently most reliable when reported

from the patients themselves. As long-term survival in cancer patients improves, the focus on treatment effects on QoL has increased. However, knowledge about QoL and the impact of treatment-related side effects in long-term survivors after RT for rectal cancer is scarce and mainly based on studies on patients treated with preoperative short-course RT (5 Gy x 5) (66). A Swedish study with 9-21 years of follow-up found that patients who had received preoperative RT scored significantly lower for social functioning and, furthermore, that patients with faecal incontinence had significantly lower QoL scores than those who were continent (82, 112). In a study of 142 patients treated with RT for gynaecological, urological or gastrointestinal tumours, about 50% suffered from bowel problems affecting their QoL 3 months or more after RT (67). On the other hand, a large randomized trial found no difference in QoL scores 2 years after treatment with or without preoperative RT for resectable cancer (98).

2. AIMS OF THE STUDY

The aim of the study was to evaluate the effect of RT on long-term functional outcome and quality of life in rectal cancer patients. Patients treated with RT and surgery (RT+) were compared with patients treated with surgery alone (RT-). The main hypothesis was that patients treated with RT had a worse functional outcome, and that a poor functional outcome had a negative impact on quality of life.

The following were the specific aims:

- To examine whether RT+ patients had more bowel, anorectal and bladder dysfunction compared with RT- patients.
- To examine whether RT+ patients had impaired QoL compared with RT- patients and also compared with the Norwegian general population, and whether a worse functional outcome affected QoL.
- To examine whether S-testosterone was reduced in male RT+ patients compared with male RT- patients, and whether hormonal status was associated with radiation-related factors.
- To examine whether RT+ patients had significantly impaired sexual function compared with RT- patients.

3. MATERIALS AND METHODS

Study population, design and data collection

Patients were sampled from a national database, the NRCR, which is part of the Cancer Registry of Norway, and includes all patients with rectal cancer in Norway diagnosed since November 1993 (23).

We identified all patients in the NRCR diagnosed with primary rectal cancer from November 1993 to December 2003 who had been treated with pre- or postoperative (chemo-) RT with curative intention and who were registered without metastasis, local recurrence or synchronous prostate cancer (RT+ patients). Only patients still alive at least 2 years after surgery were included. To serve as controls, patients treated with surgery alone (RT- patients) were sampled from the NRCR using the same criteria as the RT+ patients. The controls were drawn randomly and were not matched for age-, treatment- or disease-related factors, in order to allow analyses of the effect of these variables. Instead of matching patients to be included, potential confounding factors were adjusted for in multivariable statistical analyses.

Sample size estimation was based on QoL (measured with QLQ C-30). A difference in mean score of ≥ 10 points is considered clinically significant (113). Based on data from a previous Norwegian study of QoL in rectal cancer patients (114), we assumed a standard deviation of $SD=26$. With a power of 80% and a two-sided significance level of 5%, we estimated that at least 108 patients from each treatment group (RT+ and RT-) had to be included (114). For the LENT SOMA and sexual function data we had little prior knowledge about the distribution of the scores and sample size could not easily be calculated. As we planned to perform analyses on subsets of the data, we decided to include all RT+ patients available. Twice as many RT- patients were identified in order to increase the power of the study.

The patients were contacted by mail and invited to participate in the study. Two reminders were sent to non-responders after approximately 2 and 4 weeks. Patients who returned written informed consent participated in a structured questionnaire-based telephone interview, and they completed two self-administered questionnaires: the EORTC QLQ-C30 (all patients) and the IIEF (males) or the SVQ (females), and returned them by mail. Blood samples were drawn at the patients' general practitioner's office.

A flow chart of the inclusion process is presented on page 23. Patients were excluded if they had undergone surgery with local excision, or if they had died, moved abroad or were not

able to give informed consent due to dementia or severe illness. Furthermore, patients were excluded from the analyses if the telephone interview disclosed that they: (1) had local recurrence or current metastases at the time of the study and (2) had received pelvic RT for other malignancies. Other exclusion criteria specific for each of the papers I-IV were as given below.

Paper I

Patients were excluded from the analyses if the RT charts disclosed that they had received a total dose of <42 Gy (less than 90% of planned dose).

Paper II

Patients were excluded from the analyses if the telephone interview disclosed current or previous treatment for prostate or testicular cancer.

Paper III

Patients were excluded from the analysis if they were aged ≥ 80 years, or if the telephone interview disclosed current or previous treatment for prostate or testicular cancer.

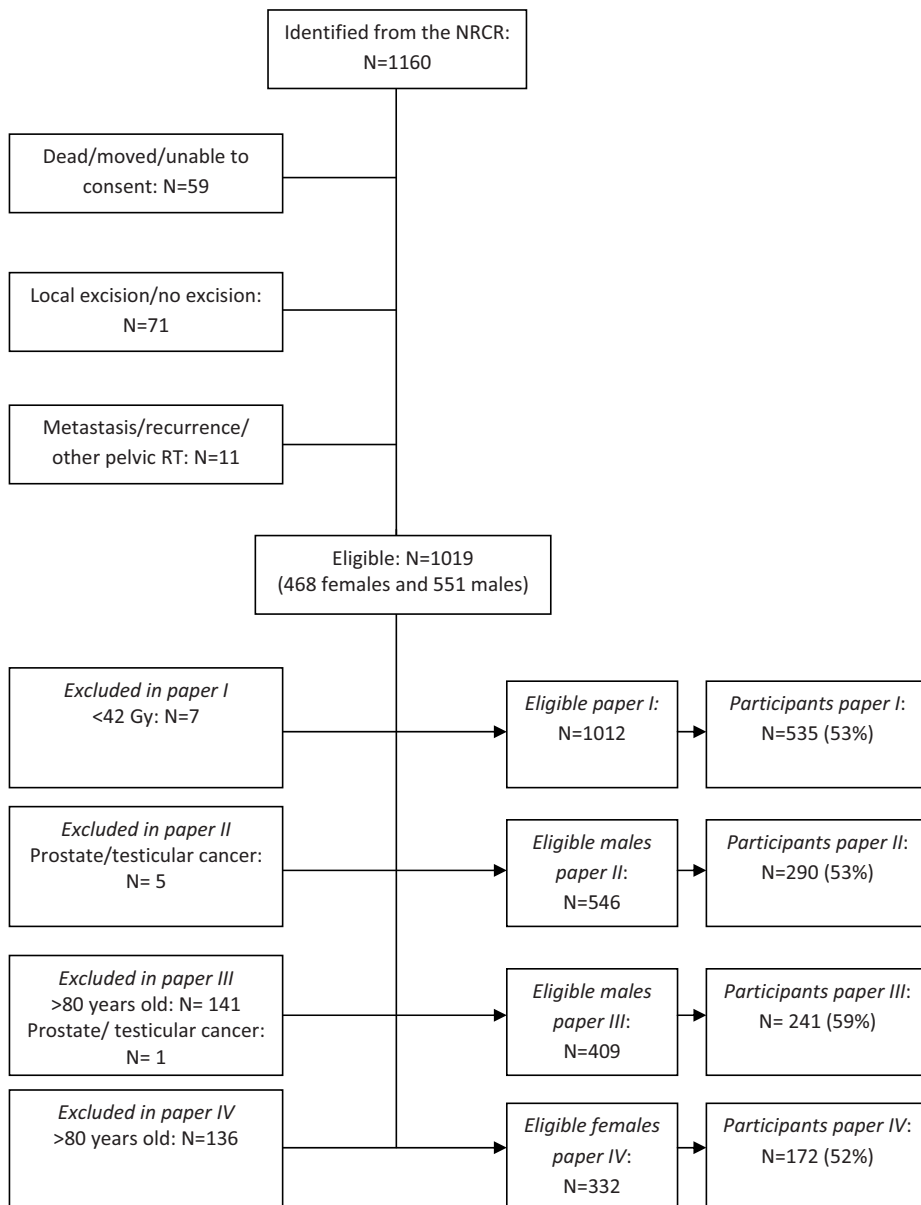
Paper IV

Patients were excluded from the analysis if they were aged ≥ 80 years.

Ethical considerations

All participating patients signed an informed consent form. The study was approved by the regional committee for Medical Research Ethics and the Norwegian Data Inspectorate.

FLOW CHART OF THE STUDY POPULATION IN PAPERS I-IV



The interview

Symptoms of late toxicity on bowel, anorectal and bladder function were assessed using the LENT SOMA scoring system (115) and the St Mark's score of incontinence (116) in a questionnaire-based, structured, telephone interview (see Appendix A). The interview also contained additional questions such as current medication, comorbidity, working status and smoking. The interview was pilot tested in 10 patients with rectal cancer to evaluate the feasibility of the interview before the study. The patient interviews were performed by a research-nurse or physician.

The LENT SOMA

The LENT SOMA is an international instrument for recording late radiation effects on normal tissue, published in 1995 by the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) (115). The instrument consists of four separate elements comprising subjective (patients' symptoms), objective (clinical examination), management (medical intervention) and analytical (objective assessment) data for all anatomical sites. In this study the questions were designed to answer the "subjective" and "management" part for the small intestine/colon, rectum and bladder/urethra.

The LENT SOMA scoring system was designed to record side effects in detail and pays attention to both the frequency and the severity of late effects. The LENT SOMA scales have not been fully validated, but have been compared with other scoring systems, such as the RTOG/EORTC late effects scoring system, and the Franco-Italian scale. It was found to be feasible for use in a clinical setting and to provide additional information on subjective treatment effects (117-120). The initial recommendation, to sum all scores for each organ and divide the result by the number of questions, was withdrawn because this method may underestimate the severity of some side effects (121). We therefore analysed the questions separately and reported the frequency of patients with a specific symptom.

St Mark's score of incontinence

The degree of faecal incontinence was assessed in the telephone interview with S. Mark's score (Table 2). St Mark's score of incontinence has been validated and shown to be reliable, sensitive and applicable to oncological patients treated with pelvic RT (67, 116, 122). The questionnaire contains seven questions about type (gas, fluid or solid) and

frequency of faecal incontinence, and alteration in lifestyle, scored on a 0- to 4-point Likert scale. Furthermore, it contains questions about the need to wear sanitary pads, use of antidiarrhoeal medication and faecal urgency. The calculated incontinence score ranges from 0 (complete continence) to 24 (complete incontinence), with the time frame being the last 4 weeks. To determine the association between RT and faecal incontinence after adjusting for potential confounding factors, we dichotomized the symptom scores into whether or not it happened more frequently than once a month.

Table 2. St Mark's score of faecal incontinence

	Never	Rarely	Sometimes	Weekly	Daily
Incontinence for solid stool	0	1	2	3	4
Incontinence for liquid stool	0	1	2	3	4
Incontinence for gas	0	1	2	3	4
Alteration in lifestyle	0	1	2	3	4
				No	Yes
Need to wear a pad or plug				0	2
Taking constipation medicines				0	2
Lack of ability to defer defecation for 15 minutes				0	4

Never = no episodes in the past four weeks; Rarely = 1 episode in the past four weeks; Sometimes = >1 episode in the past four weeks but <1 per week; Weekly = 1 or more episodes a week but <1 per day; Daily = 1 or more episodes a day. Add one score from each row: minimum score = 0 perfect continence; maximum score 24 = totally incontinent

The blood samples

Testosterone and gonadotrophins

Male patients who agreed to participate in the study (both RT+ and RT-) received a laboratory requisition, tubes for blood sampling and a letter with information about the procedure. The samples were drawn at the general practitioner's office or at the local hospital before 10am and were sent to the Hormone Laboratory at Aker University Hospital, Oslo, Norway for analysis. The tests were analysed and the results reported consecutively.

Serum-testosterone was analysed by radioimmunoassay. Serum sex hormone-binding globulin (SHBG), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were measured by immunofluorometric assay. Free testosterone values were calculated from total testosterone and SHBG, using a fixed albumin level according to Vermeulen et al. (123).

Low S-testosterone was defined as S-testosterone below the reference range (<8 nmol/L). The laboratory's reference values for FSH and LH were <12 IU/L and for SHBG 15-90 nmol/l. No reference values had been established for calculated free testosterone.

The patients' weight and height were self-reported, and the body mass index (BMI) was calculated (weight/ height x height).

The questionnaires

The QLQ-C30 (see appendix B)

The QoL was assessed by a self-administered questionnaire, the EORTC QLQ-C30 version 3.0 (124). The QLQ-C30 was developed to assess QoL in cancer patients and has been validated and tested in different cultures and in various cancer populations (124, 125). The questionnaire includes 30 questions (items) forming five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea and vomiting, and pain) and a global health status/QoL scale. Furthermore, it contains six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The time frame used is the past week.

The questions constituting the global QoL scale are scored on a modified visual analogue scale from 1 to 7. The remaining 28 questions have four response categories: "not at all", "a little", "quite a bit" or "very much". All calculations on the QLQ-C30 data were performed after linear transformation of the scores to a scale from 0 to 100. A high score on the functional scales indicates better functioning, whereas a high score on the symptom scales or single items indicates more symptoms. Missing values were handled as recommended by the EORTC Quality of Life Group (126). If at least half the items from the scale had been answered, the missing item was assumed to have values equal to the average of those items present. If less than half of items from the scale had been answered, the scale score was said to be missing. Of the 491 QLQ-C30 questionnaires returned in this study, the mean proportion of missing items was only 0.5% (range 0-1.8%).

In the current study we assessed only the function scales from QLQ-C30, because the potential late effects from RT on gastrointestinal and bladder function were covered in depth in the LENT SOMA and St Mark's Incontinence Scale. For the same reasons we did not use the QLQ CR-29, which is the colorectal module recommended as supplementary to the QLQ-C30. The function scale scores for RT+ patients were compared with the scores for the RT-patients, and with those from an age- and gender-adjusted sample of the Norwegian general

population (127). A difference in mean score of ≥ 10 was considered clinically significant, based on a study by Osoba et al., in which a change in mean score of 5-10 was interpreted as "little", 10-20 as "moderate", and >20 as "very much" (113).

Male sexual function- the IIEF (see appendix C)

Male patients were asked to complete the International Index of Erectile Function (IIEF), a questionnaire shown to have good psychometric properties (128, 129), and that has been widely used to evaluate erectile function in patients with pelvic cancer (130). The questionnaire was translated into Norwegian following a standard linguistic validation process (131).

The IIEF is a 15-item questionnaire where the responses are scored on a 5- or 6-point Likert scale, with lower scores indicating poorer sexual function. The time frame used is the last 4 weeks. The items are grouped into five domains: sexual desire, erectile function, orgasmic function, intercourse satisfaction and overall satisfaction with sex life. For each domain a summary score is calculated. Any missing response results in the patient being omitted from the final calculation of the domain score, according to the IIEF scoring manual. The erectile function (EF) score has been ranked into 5 levels according to clinical severity (129, 132). When analysing the associations between RT, patient- and treatment-related characteristics, and EF, the EF score was dichotomized into no/mild ED or moderate-to-severe ED. Questions about treatment for ED and ejaculation problems (dry ejaculation) were added. The single question about ejaculation problems was later omitted from the analyses due to a high number of missing responses.

Female sexual function - the SVQ (see appendix D)

At the time of the study, there was no comprehensive questionnaire available that assessed sexual function in women with rectal cancer. The Sexual Function and Vaginal Changes Questionnaire (SVQ) has been designed to assess sexual function and vaginal changes in gynaecological cancer patients treated with surgery and/or RT, and has been tested to establish reliability and validity (133). As we aimed to use a questionnaire that covered vaginal problems often observed after pelvic RT, this questionnaire was considered an appropriate choice. The Danish version of the SVQ was obtained from the author of the original validation study (133). A forward-backward translation was performed, and the interpretation of the final version was pilot tested in 10 female patients with rectal cancer undergoing treatment at our department.

The SVQ is a 17-item questionnaire that consists of two parts; the first is answered by all respondents and concerns intimacy, sexual interest, satisfaction with sex life/lack of sex life and worries about sex life. The second part is answered only by women who have been sexually active during the last month and includes symptom scales on vaginal changes (VC) and a scale on sexual functioning (SF). 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. Two questions are scored on a Likert scale, ranging from 1- to 7. A higher score on a symptom-scale represents more symptoms and a higher score on a function scale represents better functioning. Missing values were replaced using the same methods as in the QLQ-C30 (126, 134). Logistic regression analyses were performed to adjust for potentially confounding factors. For these analyses the answers were dichotomized into “quite a bit/very much” or “not at all/a little”. Questions about use of systemic or topical oestrogens or vaginal lubricants were added.

Statistical analyses

Most sets of continuous data in this thesis were of non-normal distribution, and the results and measures of variation were given as median (range) values. Comparisons between RT+ and RT- patients were done with the Mann-Whitney U-test for two independent samples. Differences in proportions between the two treatment groups were analysed using Pearson's chi-square and the chi-square test for linear trend if data were ordinal. All tests were two tailed, and a p value <0.05 was considered statistically significant.

In paper I, mean scores of QoL were presented although the data were not from a true continuous scale. The QoL- scores were linearly transformed into scales ranging from 0 to 100 based on two to five questions with four answer categories (none at all- a little- quite a bit- very much). With few response categories and a high proportion scoring 0 (no symptoms) or 100 (no dysfunction), the medians are rather uninformative. Due to obviously skewed distributions non-parametric tests (Mann-Whitney U test) were used for comparison between groups of patients.

Spearman's rank order correlation (ρ) was calculated to assess the relationship between the frequency of incontinence and the scores for global QoL perception and social function, because a linear relationship was not expected between the variables.

Multiple logistic regression analysis was applied to evaluate associations between RT details and patient-reported symptoms such as faecal incontinence and urinary incontinence in paper I, erectile dysfunction in paper III and vaginal problems in paper IV. Symptoms were

dichotomized according to severity and/or frequency. The strength of the association was expressed as odds ratios (ORs) with 95% confidence intervals (CI). Potentially confounding factors were identified by searching the literature and from biological considerations, and included in the analyses with multiple explanatory variables if they were statistically significant ($p < 0.05$) in separate logistic regression analyses with one explanatory variable. Generally, we avoided including a large number of covariates in the regression model and applied the rule of thumb that the number of covariates should not exceed 10-15% of the number of events (135). Due to the low number of sexually active females, fewer covariates could be used simultaneously in paper IV than in papers I-III, and the models were built by repeatedly applying separate sets of covariates and excluding those that were a long way from being statistically significant.

In paper II, the relationship between testosterone and gonadotrophins and RT was examined with multiple linear regression analyses. Potentially confounding factors were identified from a literature search and biological plausibility. The variables included in the final regression models were restricted to statistically significant covariates ($p < 0.05$) only.

Except for the confirmatory factor analysis of the IIEF, all statistical analyses were done with the latest version of the Statistical Package for Social Sciences (SPSS, Inc, Chicago, IL).

4. SUMMARY OF RESULTS

Paper I

The aims of this study were to compare patient-reported bowel, anorectal, and urinary function in RT+ and RT- patients, and to assess if anorectal or bladder dysfunction had a negative impact on social function and global quality of life and health perception (global QoL). The data on late morbidity were collected by a telephone interview, with emphasis on bowel, rectal, sphincter and urinary function. For assessment of QoL, the patients completed a self-administered questionnaire, the EORTC QLQ-C30, and returned it by mail. A total of 535 eligible patients were interviewed, after a median time since surgery of 4.8 years.

Bowel and bladder-function

RT+ patients ($n = 199$) had increased bowel frequency compared with RT- patients ($n = 336$); 19% vs 6% had more than eight daily bowel movements (LENT SOMA grade 3-4) ($p < 0.001$). In patients without a stoma, a higher proportion of RT+ ($n = 69$) compared with RT- patients ($n = 240$), were incontinent for loose stools (49% vs 15%, $p < 0.001$), needed pad (52% vs 13%, $p < 0.001$), or lacked ability to defer defecation (44% vs 16%, $p < 0.001$). After adjusting for tumor distance from the anal verge, the odds of symptoms of faecal incontinence in RT+ patients was still three to seven times higher than in RT- patients, and the mean incontinence score was significantly higher in RT+ than in RT- patients (9.2 vs 3.9, $p < 0.001$). In patients without a stoma, a higher proportion of RT+ compared with RT- patients had loose or liquid stool (36% vs 16%, respectively, $p < 0.001$). There were no statistically significant differences in the proportion of RT+ vs. RT- patients reporting rectal pain (13% vs. 6%, respectively, $p = 0.06$) or blood in the stools (9% vs 6%, respectively, $p = 0.27$) over the last month.

Urinary incontinence was more common in RT+ than in RT- patients (36% vs 24%, $p = 0.02$). Daily urinary incontinence (LENT SOMA grade 3) was less frequent, but occurred more often after RT (9% in RT+ vs 2% in RT-, $p = 0.001$). There was no association between urinary incontinence and ypT- stage or tumour height above anal verge, or type of resection (AR/APR). There were no significant differences in voiding frequency, haematuria or dysuria between the two treatment groups.

Quality of life

In the interview, 15% of the RT+ patients without stoma, compared with 4% of the RT- patients, answered that their bowel function resulted in major restrictions in their social life (p

= 0.003). According to the QLQ- C30 data, RT+ patients had significantly impaired social function compared to the RT- patients (mean 70 vs 82, $p < 0.001$), as well as compared with age- and sex-adjusted values from the Norwegian general population. There were no differences in the remaining function scales.

Patients who suffered from faecal incontinence weekly or more often had significantly impaired scores for social function and global QoL compared with continent patients. Also, patients with reduced ability to defer defecation, or patients using constipating medication, had significantly lower mean scores for social function and global QoL. The impairments in mean scores were between 10- and 20 points, a clinically moderate difference. Urinary incontinence of any grade did not affect QoL- scores, but the small subgroup of patients with daily episodes had significantly lower scores for several function scales.

Conclusions: RT for rectal cancer is associated with considerable long-term effects on anorectal function, especially in terms of increased bowel frequency and increased risk of faecal incontinence. RT+ patients reported lower scores for social function, and faecal incontinence had a negative impact on QoL.

Paper II

The aims of the study were to examine whether RT for rectal cancer was associated with reduced S-testosterone and whether male hormonal status was associated with RT treatment-related factors. Blood tests were received from 290 men, 116 RT+ and 174 RT- patients, and the median age was 66 years and 71 years, respectively.

In the RT+ group, 27% of patients had S-testosterone levels below the reference range (8–35 nmol/L), compared with 10% of the RT- patients ($p < 0.001$). RT+ patients had lower S-testosterone (mean 11.1 vs 13.4 nmol/L, $p < 0.001$) and lower calculated free testosterone (mean 214 vs 235 pmol/L, $p < 0.05$) than RT- patients. When adjusting for age and BMI, the mean S-testosterone level among RT+ men was 2.7 nmol/l (95% CI= -1.5 to -3.9), lower than in RT- men, a reduction of 20%. Serum FSH was three times higher in the RT+ group than in the RT- group (median 18.8 vs 6.3 IU/L, $p < 0.001$) and serum LH was 1.7 times higher (median 7.5 vs 4.5 IU/l, $p < 0.001$).

The levels of total S-testosterone, calculated free testosterone and gonadotrophins were related to the distance from the bony pelvic structures to the caudal field edge. Multiple regression analysis showed a significant association between lower caudal field edge and

lower S-testosterone, signifying that the proximity of the testicles to the radiation field impacts on testosterone levels. Treatment with two-field technique was significantly associated with reduced S-testosterone levels compared with three fields or more.

Conclusions: Increased serum levels of gonadotropins and subnormal serum levels of testosterone indicate that curative RT for rectal cancer can result in permanent testicular dysfunction.

Paper III

The primary aim of this study was to compare self-rated sexual functioning, in male patients who had surgery for rectal cancer and either RT or no RT, using an instrument with established psychometric properties, at least 2 years after surgery. As we had previously shown that RT for rectal cancer can lead to permanent reduction in S-testosterone, we also wanted to examine whether the reduced S-testosterone was associated with erectile dysfunction. Questionnaires (IIEF) were returned from 241 patients a median of 4.5 years after surgery. The median age was 67 years.

RT+ patients ($n = 108$) had significantly poorer scores for erectile function, orgasmic function, intercourse satisfaction and overall satisfaction with sex life compared with RT- patients ($n = 133$). In multiple, age-adjusted analysis, the odds ratio for moderate-to-severe erectile dysfunction in RT+ patients was 7.3 compared with RT- patients (CI = 3.3-16.0, $p < 0.001$). Moderate-to-severe erectile dysfunction was associated with low S-testosterone (CI (OR) = 1.5-32.5, $p = 0.01$).

Conclusions: RT for rectal cancer is associated with significant long-term effects on male sexual function, especially in terms of erectile dysfunction.

Paper IV

The purpose of this study was to compare self-rated sexual function in female patients who had surgery for rectal cancer and either RT or no RT, at least 2 years after surgery. We aimed to use a questionnaire designed for use in female cancer patients, to assess side effects from pelvic radiotherapy in women. Questionnaires were returned from 172 patients, a median of 4.5 years after surgery. The median age was 65 years.

Among the responding RT+ patients ($n = 62$) and RT- patients ($n = 110$), there were no differences in the frequency of being sexually active, in sexual interest or in worries about sex life. In sexually active women ($n = 55$), 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.

Conclusions: The present study indicates that women treated for rectal cancer with pre- or postoperative (chemo-) RT and surgery have an increased risk of vaginal problems at long-term follow-up, compared with women treated with surgery alone. However, to what extent these symptoms have an impact on sexual function is not clear.

5. DISCUSSION

Methodological considerations

Among the strengths of this study is the use of a national cohort, because all patients alive who had been treated with RT for rectal cancer in the period 1993-2003 were identified. The access to treatment- and cancer-specific data from the Norwegian Rectal Cancer Registry, and data from the patients' RT hospital- charts, along with patient-reported outcomes, made a comprehensive analysis possible.

In clinical trials, analytical data (laboratory/imaging) are preferred endpoints because these can be validated across observers. Semiquantitative observer-based measures such as endoscopic findings, histological changes and physiological tests are also important in the understanding of the pathogenesis of radiation side effects. Nevertheless, these findings do not always correlate well with the patient's symptoms (136, 137). Despite a low specificity in patient-reported outcomes and QoL, these are often the most relevant endpoints to the patient (Figure 4). This trade-off between patient relevance and specificity has been described by several authors (138, 139).

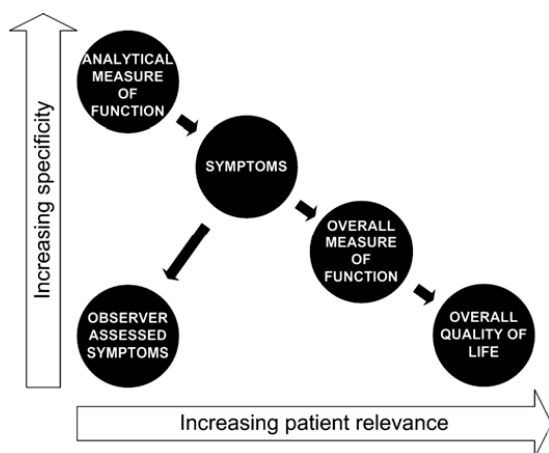


Figure 4. Illustration of the trade-off between specificity and patient relevance of different measures of side effects (with permission from K. Jensen) (139)

Patient-reported symptoms are often underreported or underestimated in clinical trials (140, 141). Furthermore, less severe morbidity, such as occasional faecal incontinence, may be

undetected in retrospective studies of hospital charts, as these rarely result in admittance to hospital. Reporting of treatment-related morbidity is also highly dependent on the methods used. This was demonstrated by one study, which uncovered 22 times more adverse events when using a detailed patient-reported questionnaire compared with unstructured reporting (142). Ideally, validated scoring tools are preferable; however, most physician-scored toxicity scales have not been formally validated. We therefore aimed to use a structured and detailed questionnaire, which was based on relevant and widely accepted scoring systems, for assessing late morbidity in bowel and bladder.

Prolonged observation is necessary because late morbidity after RT has shown a wide range of latency times, and may not become clinically manifest until several years after treatment. One of the strengths of this study is the follow-up time since treatment of between 2 and 13 years. Only a few studies have evaluated late adverse effects more than 2 years after RT with 50 Gy in rectal cancer patients (40, 42, 76, 143, 144). Most of these studies were conducted before the introduction of modern surgery (TME and stapling technique) and had used a different RT regimen.

In a cross-sectional study, only a “snap-shot” of the patients’ situation was obtained with no information about changes over time or the sequence in the time of the development of symptoms and the exposure (RT). It is therefore not possible to establish causal relationships from the current study. A prospective design would have provided more information about the time factor and the actual number of patients at risk, and such studies should be conducted in the future.

Selection bias

In this cross-sectional study, the patients and disease- and treatment-related data were sampled from a large, unselected, national patient registry, the Norwegian Colorectal Cancer Registry. However, because of the study design, the clinical picture in patients who have deceased or developed metastases is unknown, and the results should therefore be interpreted with caution. In attrition analyses, the responders and non-responders did not differ with regard to type of surgery, whether or not RT was used, T-stage or treating hospital, but responding patients were younger and had a shorter time since surgery. One explanation might be that patients treated several years ago consider themselves “healthy” and do not want to attend the study and thereby be “reminded” of the disease; in that case symptoms may be overreported. On the other hand, older non-responders might have more

morbidity, making them less capable or willing to participate. In that case, side effects might have been underreported.

The study had a fairly low response rate among patients aged older than 70 years, and the results in the oldest age group are therefore prone to be affected by selection bias. Non-responders tend to be less healthy in questionnaire-based surveys (145) and this may have led to an underestimation of health problems in both groups of patients. However, when the analyses for bowel function, urinary function and QoL were repeated, excluding patients aged over 70, the estimated differences between RT+ and RT- patients remained unchanged.

Confounding factors and sample size

As a result of the study design, there were differences in tumour characteristics between the two treatment groups. Patients were treated with RT preoperatively because of T4 tumour, tethered tumour, potentially threatened resection margins or postoperatively because of involved resection margins. Furthermore, RT+ patients had tumours closer to the anal verge and were more often treated with chemotherapy. When designing the study we chose not to match for potentially confounding factors, because variables used for matching cannot later be investigated as possible risk factors. Instead, confounding factors (identified from both searching the literature and biological considerations) were adjusted for in multiple regression analyses. Nevertheless, there are some limitations to this strategy; the possibility for adjusting for confounders is limited when the event is rare; as a rule of thumb the number of covariates in a regression model should not generally exceed about 10-15% of the number of events. Furthermore, in analyses with using low numbers of patients, there is a risk of not detecting existing differences (type II statistical error). These problems are particularly relevant in papers III and IV as the numbers of patients who had been sexually active were limited in this elderly population.

An important possible confounding factor is the fact that about half the irradiated patients had received concomitant chemotherapy. 5-FU-based chemotherapy is known to increase the acute toxicity in rectal cancer treatment (50). Few studies have assessed this issue in long-term follow-up. A Polish study compared short-course RT with CRT and found no difference in QoL or in late toxicity after 4 years of follow-up (49).

Information bias

Information bias may occur if the reliability of the information or data differs systematically between patients and controls. In this study, the interviewer was not blinded to whether patients had been treated with RT, which may have led to a worse scoring of exposed patients. However, the interview was based on a structured questionnaire with given response alternatives for most of the questions, e.g. the patients were asked if their daily defecation frequency was 0-1, 2-4, 5-7, >8 or uncontrolled diarrhoea. Furthermore, none of the three interviewers had treated the patients in the study, thereby avoiding a situation where patients could theoretically give “pleasing” answers. For the self-administered questionnaires, we used questionnaires that had been extensively validated and translated according to international standards.

To reduce inaccuracy in recalled information, we used the time frame of 1 month for the questions about bladder and bowel function and did not ask the patients to compare symptoms or function with how it was before the cancer treatment.

Discussion of the main findings

Bowel, anorectal, and bladder function

In paper I we found that RT for rectal cancer was associated with considerable late side effects on bowel and anorectal function, especially in terms of increased bowel frequency, urgency and faecal incontinence.

In patients without a stoma, 49% of the irradiated versus 15% of the non-irradiated patients were incontinent for liquid stools, 52% versus 13%, respectively, needed pads and 44% vs 16%, respectively, lacked the ability to defer defecation. These findings are quite similar to those of other studies. In the Stockholm Radiotherapy Trials (25 Gy), the frequency of faecal incontinence was 57% in irradiated ($n = 21$) and 25% in non-irradiated patients ($n = 43$) 14 years after treatment (112). The Dutch TME study found a frequency of faecal incontinence of 62% in the preoperative RT- arm and 38% in the surgery-alone arm after a follow-up of 5 years. There are only a few reports on long-term morbidity in bowel and anal function after RT with 50 Gy. In a retrospective, single-centre study comparing patients treated with postoperative CRT with patients treated with surgery alone, Kollmorgen et al. reported increased frequency of daily bowel movements (7 vs 2, respectively), more faecal incontinence (39% vs 17%, respectively) and a higher proportion of patients unable to defer defecation 15 minutes (78% vs 19%, respectively) (76). Another Danish study with a follow-

up of 11-20 years found that patients who had undergone postoperative RT had significantly increased stool frequency and more often liquid stool, and a higher proportion had faecal incontinence and used pads (143, 144).

As only high-risk patients received RT, the two treatment groups in our study were different in many respects. RT+ patients had a higher prevalence of tumours situated in the distal rectum, and a higher proportion had stage pT3-4 tumours. We found a significant effect of tumor height on faecal incontinence in analysis with multiple explanatory variables. Tumour height and level of anastomoses as risk factors for faecal incontinence have been studied by others. In a previous study from the Norwegian Rectal Cancer Registry, patients with very low anastomoses (≤ 3 cm from anal verge) had more incontinence than patients with higher anastomoses, but there was no linear relationship between the two (114). In the TME study (146), Lange et al. observed that, in the RT group, but not in the surgery-alone group, patients with tumours closer to the anal verge had an increased risk of faecal incontinence compared with patients with higher situated tumours. In this study tumour height determined the lower border of the radiation field, and the data also showed an increased risk of faecal incontinence (relative risk 7.45, $p = 0.059$) in patients where the perineum was included in the radiation field. In the Swedish Rectal Cancer Trial, anastomotic height had no effect on bowel function in the long-term follow-up (75).

T-category, on the other hand, was not a significant covariate for either faecal or urinary incontinence in analyses with multiple explanatory variables. As a result of the low number of T4 tumours in the control group ($n = 7$) we also analysed T-category as a dichotomized variable (T1 and T2 tumours or T3 and T4 tumours); however, this did not change the outcome. There was no effect of TNM stage on the risk for faecal incontinence in either the TME study or the Swedish Rectal Cancer Trial. However, in both the Dutch and the Swedish trials, only primarily resectable cases were included, whereas our study also included patients with tumors that were not primarily resectable (T4 and tethered tumours). In another study, 43 disease-free patients, previously treated with extended TME and RT for locally advanced or locally recurrent tumours, reported more defecation problems and pain, and lower scores for several QoL scales compared with patients with primarily resectable tumours (147).

It is well known that surgery for rectal cancer may have significant morbidity in relation to bowel and bladder function (148, 149). However, with a median follow-up time of almost 5 years since surgery, the side effects of surgery were expected to have stabilized. This is supported by the findings in the Dutch TME study: at follow-up during the first 2 years after

treatment, the percentage with faecal incontinence decreased significantly in patients treated with RT as well as in patients treated with surgery alone and, except for a slower recovery of bowel function, there were few differences in QoL between patients treated with and those not treated with RT (98). However, comparing the results at 2 and 5 years of follow-up, the percentage of patients with incontinence had increased significantly in the RT group (from 52% to 62%), but not in the surgery-alone group (36% and 39%, respectively) (77, 146). Furthermore, the degree of incontinence was worse in the RT group compared with the surgery-alone group.

Quality of life

The QoL analysis did not demonstrate major differences between patients who were RT+ and RT-. Similarly, no major differences were detected when the RT group was compared with age- and gender-adjusted values from the general population. Nevertheless, irradiated patients had impaired social function compared with non-irradiated patients, and patients with frequent faecal or urinary incontinence had impaired scores for several aspects of QoL. Impaired social function in RT+ patients is quite in accordance with data from the Swedish Rectal Cancer Trial. Similar to us, they found only small differences in scores on the QLQ-C30 between RT+ and RT- patients, and between the study population and norm data from the Swedish population (82). The authors also demonstrated that patients with faecal incontinence had significantly impaired scores for all four subscales of the "Fecal incontinence quality of life"- scale (112). Also, in the Dutch TME study, the authors found no difference in QoL between patients treated or not treated with RT (98). However, the study used another questionnaire, the Rotterdam Symptom Check List, and social function was not assessed.

In our study, a higher percentage of RT+ compared with RT- patients had a permanent stoma. Some previous studies have demonstrated that patients with colostomy have impaired QoL (150, 151); others have found no difference or even better QoL scores in stoma compared with non-stoma patients (114, 152, 153). In our study, a stoma was not associated with impaired QoL. On the contrary, stoma patients reported fewer limitations in their social lives than patients without a stoma. One explanation may be that patients with a well-functioning stoma are less "toilet-dependent" than patients with various degrees of faecal incontinence. In Norway, stoma patients are followed closely and specially trained "stoma-nurses" are available to many patients for advice and assistance. In addition the patients in our study have had some time to adapt to living with a colostomy.

Several other studies have shown no or minor differences in QoL of a cancer population and a healthy “normal” population. This phenomenon, referred to as “response shift”, is often attributed to the fact that patients adapt to their situation over time, and that their perceptions of QoL may change (154), e.g. some patients might consider living with a stoma to be a small price for being cured from a life-threatening malignant disease, leading to a “recalibration” of their own internal standards and values.

Male sex hormones

The results in paper II indicate that pelvic RT for rectal cancer increases the risk of permanent testicular dysfunction, in terms of elevated levels of gonadotrophins along with a less pronounced decrease in S-testosterone. To our knowledge this is the first report on male sex hormones in long-term follow-up after RT for rectal cancer.

Recently, two Canadian publications have assessed these questions and reported similar results. One prospective study in 43 men reported an almost fivefold peak in FSH levels and doubled LH levels, in a follow-up period of 6 years after CRT for rectal cancer (155). The mean testosterone level decreased throughout follow-up from 15.4 nmol/L pre-treatment, to 11.9 nmol/L at 13-24 months and 8 nmol/L more than 48 months after CRT. The patients had been treated with a three- or four-field technique, and with doses of 1.8 Gy to a total dose of 54 Gy, and the median dose to the testicles was measured (in five patents) to 4 Gy (range 1.5-8.9). In another study, 51 patients treated with conventional external beam CRT (45-50.4 Gy) were compared with 38 patients treated with brachytherapy at a high dose-rate (26 Gy over four daily treatments of 6.5 Gy) (156). Two years after treatment, gonadotrophins were elevated in all patients, but more pronounced in the CRT group. The mean cumulative dose to the testicles in the two groups was 1.24 Gy and 0.27 Gy, respectively.

Chemotherapy, most commonly 5-FU, was given with RT in 30-100% of the patients in the above-mentioned studies. FLV was given with RT to 53% of the patients in our study and we found no association between testosterone level and chemotherapy. One animal study observed decreased testosterone values and degeneration of the seminiferous epithelium in rats treated with 5-FU, but no histological changes were observed in the Leydig cells (157). The long-term toxicity of 5-FU on the Leydig cells in humans is unclear, and there is, at the present time no knowledge about the impact of more potent chemotherapy on gonadal function.

Male sexual function

The mean score for erectile function was poor in both treatment groups (RT+ and RT-). This was not unexpected because rectal cancer surgery may cause damage to pelvic autonomic nerves resulting in erectile dysfunction (ED) and/or retrograde ejaculation (105, 158-160). However, males treated with RT and surgery had significantly poorer scores for erectile function, orgasmic function, intercourse satisfaction and overall satisfaction with sex life, but not for sexual desire, compared with men treated with surgery alone. The negative association between RT and erectile function remained significant when adjusting for possible confounding covariates such as age, type of surgery (AR or APR), T-stage and tumour height. ED is a well-known sequela after pelvic RT for prostate cancer. However, it is still debated whether ED after pelvic RT for prostate cancer is due to sequelae to the pelvic arteries, the veno-occlusive mechanisms in the corpora cavernosa or to the neurovascular bundles (161, 162).

To our knowledge, this is the first report on male sexual function after RT with 50 Gy assessed with a comprehensive questionnaire using established psychometric properties. The IIEF has been widely used in clinical trials and translated into many languages, among them Norwegian. However, in our experience the questionnaire has some limitations. Ejaculatory disorders, which have been reported after rectal cancer treatment (98), are not assessed. Furthermore, relationship-related issues are not covered in the questionnaire, making it difficult to differentiate between men who are sexually continent because of ED and those abstaining from sexual intercourse for partner-related reasons (e.g. partners with poor health, being a widower, etc.). The Male Sexual Health Questionnaire (MSHQ) was developed in 2004 to address these limitations (163), but the questionnaire was not available in Norwegian at the time of the study.

ED is a disorder with a high prevalence and the incidence increases steadily with age (164, 165). Furthermore, the ageing process in males is accompanied by a decline in S-testosterone (166). The interrelationship of RT for rectal cancer, testosterone and erectile function has to our knowledge never previously been assessed. We found that moderate-to-severe ED was statistically significantly associated with low S-testosterone in multivariable analysis with RT, age and S-testosterone as explanatory variables (OR = 6.3, CI = 1.5-32.5). Nevertheless, because of the broad confidence interval this finding should be interpreted with caution. Androgens act at several sites in the sexual response system: within the central nervous system and peripheral nerves, and finally a direct effect of androgens on the corpora cavernosa (87, 167, 168), although contradictory results exist (169). Recent studies have shown that ED is associated with both physical and mental health, indicating that sexual

function is complex, and ED is not easily attributed to a single pathogenic cause (170). However, information before treatment about an increased risk of hypogonadism and sexual dysfunction is warranted.

Female sexual function

RT+ women reported significantly more vaginal problems in terms of vaginal dryness, dyspareunia and reduced vaginal dimension, but not impaired sexual interest or more worries about sex life compared with women treated with surgery alone.

It is known that radiation to the internal female genitals may lead to vaginal atrophy, fibrosis and adhesions of the vaginal wall (102, 171, 172). Narrowing and shortening of the vagina may evolve, often together with pelvic fibrosis and loss of vaginal elasticity. Furthermore, menopause is associated with vaginal atrophy and dyspareunia, and radiation-induced ovarian failure is inevitable in premenopausal women, because the ovaries are located in the radiation field.

Only one large randomized trial, the Dutch TME study, has assessed sexual function in women after RT for rectal cancer (98). They found that RT was associated with sexual dysfunction, similar to our study. However, in contrast they found no increase in vaginal dryness or dyspareunia, but a decrease in sexual interest, pleasure and satisfaction. The Dutch study was conducted from 3 months- to 24 months after treatment, whereas our results were based on questionnaires completed 31-125 months after treatment. The time since RT may have influenced the results, as radiation late effects could have long latency times. Another difference between the two studies was that, although CRT was not used in the Dutch study, chemotherapy with 5-FU was given together with RT to 63% of the women in our study. Chemotherapy with 5-FU may in theory enhance the late effects of RT on the vaginal mucosa; however, this has to our knowledge not been documented. An independent effect of chemotherapy on vaginal changes could not be shown in the current study.

The low numbers of sexually active women limits the possibilities of adjusting for potentially confounding factors in this study. Furthermore, the SVQ measures vaginal symptoms in sexually active women only, and gives no information about symptoms in women who had not had recent sexual intercourse. It is possible that the women, who had not had intercourse have vaginal problems that have not been reported.

Prevention of side effects

The most important method of decreasing the irradiation dose to the small bowel during pelvic RT is the use of multiple radiation fields. Treatment with three to four fields significantly decreases the volume of small bowel compared with a two-field technique, and is now considered standard treatment in most countries. Other measures that have been taken to reduce the dose to the small bowel are: patient treatment in a prone position, the use of a belly board, and patient instructions to drink water to increase the bladder filling (173).

For patients with tumours situated in the upper part of the rectum, who are treated with sphincter-preserving surgery, the caudal field edge should be placed so that the sphincter is spared. Al-Abany et al. found a dose-volume effect between the dose to the anal sphincter region and the risk of faecal leakage in 65 patients with prostate cancer (174). However, the functional tolerance dose of the anal sphincter is not known, and faecal continence is also dependent on the capability of the rectum to act as a reservoir. A decrease in rectal compliance is often seen after RT for rectal cancer because the rectum is part of the target volume for radiotherapy (175), but is also seen after complications of surgery (176).

To reduce the testicular dose, treatment using the centre of the radiation field placed far caudal in the target (half-beam technique) was recently compared with standard treatment technique in a study on 22 patients from our institution (177). An average 48% reduction in testicular dose was achieved, while the dose to the target volume was maintained. A half-beam technique is simple to use, and could be an alternative or supplement to other methods for reducing testicular dose; however, the method needs further validation. Others have suggested the use of a double-hole belly board or a lead shield (178-180). These techniques have not been integrated into clinical practice in the treatment of rectal cancer, and so effect in preventing testicular dysfunction is not known.

The dose-volume relationship in ED is not established. Exclusion of the penile bulb, neurovascular bundles, penile crura or corpora cavernosa of the radiation field has been suggested, but the results are inconsistent (181).

Prevention of radiation-induced vaginal stenosis is facilitated with the use of vaginal dilators and such devices should therefore be recommended (182). The evidence for use of topical oestrogens to prevent vaginal bleeding and dyspareunia is less clear and needs to be confirmed in larger studies.

Currently, with the use of intensity-modulated radiotherapy (IMRT) it is possible to create a more conformal treatment plan that has a similar target coverage and a large reduction in

dose to the organs at risk (OAR) compared with conventional techniques (183, 184). However, IMRT will inevitably increase the irradiated volume in the low-dose range because of the use of multiple fields and the impact on late morbidity, in particular the risk of secondary cancers, needs to be further studied.

6. CONCLUSION

Improvements in treatment of rectal cancer have resulted in reduced frequency of local recurrence and an increasing number of long-term survivors. In Norway, a larger proportion of patients have been treated with preoperative RT over the last few years. The papers of this thesis have focused on late morbidity and quality of life in long-term survivors after RT for rectal cancer.

We found that RT+ is associated with considerable late side effects on bowel and anorectal function, especially in terms of increased bowel frequency and increased risk of faecal incontinence. In particular, the risk of incontinence for loose stools, the need for sanitary pads and faecal urgency were higher in patients treated with compared with those not treated with RT. Urinary incontinence also occurred more frequently in RT+ compared with RT- patients.

More male RT+ than RT- patients had increased levels of serum gonadotrophins and subnormal levels of serum testosterone, indicating permanent testicular dysfunction. Further studies are needed to evaluate the impact of Leydig cell dysfunction on morbidity and quality of life in these patients.

The risk of male sexual dysfunction, in particular moderate-to-severe ED, was high in both treatment groups; however, it was significantly higher in RT+ compared with RT- patients. Female RT+ patients more often experienced vaginal problems than women treated with surgery alone. No impairment in sexual function was disclosed in women treated with RT. More studies are needed in order to clarify the effect of RT on female sexual function.

Global QoL was not impaired in RT+ patients compared with either RT- patients or values from the general Norwegian population. However, RT+ patients had lower scores for social function, compared with either patients treated for rectal cancer with surgery alone or with the general population. Patients with faecal incontinence had impaired scores for several aspects of QoL compared with continent patients.

7. FUTURE PERSPECTIVES

Cancer treatment, including surgery, RT and chemotherapy, are associated with a spectrum of normal tissue effects and there is no therapeutic gain unless advances in tumour control are balanced against the treatment-related morbidity. As improvements and changes in the treatment of cancer result in large numbers of long-term survivors, knowledge about patients' QoL becomes increasingly important. The study of normal tissue side effects from RT should be an integrated part of the quality assurance of cancer treatment. Information must be prospectively collected and include patient-reported as well as physician-assessed morbidity. As RT is often part of a multimodality treatment, side effects from surgery and chemotherapy need to be assessed as well. Uniformity in reporting side effects increases the value of the data, and standardized reporting should be preferred. Further studies are needed to establish the dose-volume relationship for late morbidity and, furthermore, to develop strategies for prevention and treatment of these.

Errata

Paper I: *Study design*: “we identified all male patients” should be “we identified all patients (male and female)”....

Paper II: Identified male patients should be 620 and eligible male patients 546.

Erratum list for

“Late side effects and quality of life after radiotherapy for rectal cancer”

-Page 5, line 6: the correct meaning of the abbreviation CRM is “circumferential *resection* margin”.

-Page 11, line 23: “...the Cancer Registry of Norway, to which all cancers in Norway are reported.” (the word *institution* is omitted)

-Page 32, line 17-18: “ The aims of the study were to examine whether RT for rectal cancer was associated with reduced S-testosterone and *whether* male hormonal status was associated with RT treatment-related factors.” (the word *both* is omitted and *whether* is added)

- Page 37, line 24: the correct numbers are papers *III* and *IV*

-Page 40, line 16: the correct name is The Swedish Rectal *Cancer* Trial

-Page 43, line 17: “...., but a decrease in sexual interest, pleasure and *satisfaction*.” (the word *dyspareunia* is omitted and *satisfaction* is added)

Kjersti Bruheim

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Sexual Function in Females after Radiotherapy for Rectal Cancer

Kjersti Bruheim, M.D.,¹ Kjell Magne Tveit, M.D., Ph.D.,^{1,2}, Eva Skovlund, Ph.D.,³ Lise Balthesgard, M.D., Ph.D.,^{4,5} Erik Carlsen, M.D., Ph.D.,⁶ Sophie D. Fosså, M.D., Ph.D.,^{7,2} Marianne G. Guren, M.D., Ph.D.,¹

¹The Cancer Centre, Oslo University Hospital, Ullevål, Oslo, Norway

²Faculty of Medicine, University of Oslo, Oslo, Norway

³School of Pharmacy, University of Oslo, Oslo, Norway

⁴Department of Oncology, University Hospital of Northern Norway, Tromsø, Norway

⁵Norwegian Gastrointestinal Cancer Group

⁶Department of Gastrointestinal Surgery, Oslo University Hospital, Ullevål, Oslo, Norway

⁷Department of Clinical Cancer Research, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway

Corresponding author

Kjersti Bruheim MD

The Cancer Centre, Oslo University Hospital, Ullevål, 0407 Oslo, Norway

Phone: +47 23 02 66 00 Fax: +47 23 02 66 01

E-mail: Kjersti.bruheim@medisin.uio.no

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Abstract

Background: Knowledge about female sexual problems after pre- or postoperative radiotherapy (RT) 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 RT (RT+ vs RT-), at least two years after surgery for rectal cancer.

Methods and materials: All surviving 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 out 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: Several years after curative surgery for rectal cancer, vaginal problems are more often reported by women who had additional RT than by patients treated with surgery alone. Information about the increased risk of side effects affecting sexual function should be provided to these patients.

Introduction

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].

Pelvic radiotherapy may cause adverse effects in normal tissue [6]. Clinical studies have shown that patients treated with radiotherapy for cervical cancer have an increased risk of vaginal problems and sexual dysfunction [7-9]. Furthermore, it has recently been shown that patient-reported symptoms are often underestimated by physicians [10].

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 x 5) had a negative impact on sexual activity and sexual function [11,12]. An American study suggested that female rectal cancer patients treated with radiotherapy had a 4-fold increase in dyspareunia compared to surgery-only patients [13]. With exception of intercourse frequency, binary (yes/no) outcomes were recorded. The response rate for questions about sexual function was 40-50 percent. 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 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

For this cross-sectional study, 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). 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 function

The SVQ is a 17-item questionnaire designed and previously validated to assess sexual function and vaginal changes in patients with gynaecological cancer [14]. 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 10 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 1). 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 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 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 3 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 [15,16]. 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 chi-square 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 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 [17].

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, 5 recurrence or pelvic RT for another malignancy and 155 age ≥ 80 years); thus 332 women were eligible. Of these, 172 women (52%) returned completed questionnaires (62/118 RT+ and 110/214 RT-); however, not all questions was 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 2). 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.

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 RT+ patients (63%); all had 5 FU based chemotherapy, and in 3 patients oxaliplatin was also given. Chemotherapy was given to 18 of the patients (55%) who received preoperative radiotherapy, and to 21 of the 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 3). 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 3). However, there was no significant difference in the score for sexual functioning (SF) 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 4). 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 4).

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 was 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 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 [6]. 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 [18]. The majority of the women diagnosed with rectal cancer have already reached the age of menopause; however, in premenopausal women radiation-induced ovarian failure may contribute to vaginal dryness and dyspareunia [19].

Sexual function has been investigated in women treated with radiotherapy for cervical cancer [20]. A prospective study by Jensen et al observed persistent sexual dysfunction and adverse vaginal changes two years after radiotherapy for cervical cancer [8]. 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 [9]. 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 [21].

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 [3,22-24]. To our knowledge only one large, randomized trial has assessed sexual function in women after RT for rectal cancer [12]. The authors found that preoperative RT (5 Gy x 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 [12]. The data were collected prospectively 3 to 24 months after radiotherapy, while the present results are based on a questionnaire completed 31-125 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 tumour 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. Only about one third of the women had been sexually active the last four weeks, which is not unexpected in this elderly population. Others have found that patients who underwent APR were less sexually active, and that having a stoma was associated with sexual dysfunction [11,13].

Like in many other studies of this intimate subject, the study had a fairly low response rate [1,9,25] 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. 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 [26]. 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 [26]. Several non-randomized studies have shown promising results using hyperbaric oxygen in cases of radio necrotic injuries to the perineum and vagina [26]. 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

There is an increased risk of dyspareunia and vaginal dryness in women following surgery combined with radiotherapy for rectal cancer than observed after surgery alone. Patients should receive information about the risk, and be encouraged to seek medical advice if needed.

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Table 1: 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
1

A little
2

Quite a bit
3

Very much
4

Table 2. Patient characteristics of responding patients

	RT+ group	RT- group
	N=62	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)
Tumour 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)

Table 3. Sexual function and vaginal changes scores in RT+ and RT- patients

Scales	Range	n (RT+/RT-)	RT+ group	RT- group	p^*
			Mean (SD)	Mean (SD)	
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 4: 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	<i>p</i>	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

Appendix A

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24. Har du lekkasje av avføring hvis den er fast?

- 1. Aldri
- 2. Sjelden (en gang eller sjeldnere pr. måned)
- 3. Noen ganger (mer enn en gang pr. måned, men sjeldnere enn en gang pr. uke)
- 4. Ukentlig
- 5. Daglig

25. Har du lekkasje av avføring hvis den er løs?

- 1. Aldri (dersom aldri både på spørsmål 24 og 25, gå videre til spørsmål 29)
- 2. Sjelden (en gang eller sjeldnere pr. måned)
- 3. Noen ganger (mer enn en gang pr. måned, men sjeldnere enn en gang pr. uke)
- 4. Ukentlig
- 5. Daglig

26. Når på døgnet har du hatt lekkasje av avføring?

- 1. Om dagen
- 2. Om natten
- 3. Både dag og natt

27. Har du måttet bruke noen form for sanitetsbind/bleie på grunn av avføringslekkasje?

- 1. Nei
- 2. Ja

28. Medfører avføringslekkasje begrensinger i dagliglivets aktiviteter (som f.eks. jobb, fritidsaktiviteter eller husarbeide?)

- 1. Aldri
- 2. Sjelden (en gang eller sjeldnere pr. måned)
- 3. Noen ganger (mer enn en gang pr. måned, men sjeldnere enn en gang pr. uke)
- 4. Ukentlig
- 5. Daglig

29. Har du problemer med å holde på luft (flatulens)?

- 1. Aldri
- 2. Sjelden (en gang eller sjeldnere pr. måned)
- 3. Noen ganger (mer enn en gang pr. måned, men sjeldnere enn en gang pr. uke)
- 4. Ukentlig
- 5. Daglig



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30. Hvor lenge kan du holde avføringen hvis det ikke er toalett i nærheten?

- 1.15 minutter eller lengre
- 2.Mindre enn 15 minutter

31. Har du forsnevring på endetarmen?

- 1.Nei
- 2.Ja, må benytte spesiell diett
- 3.Ja, har blitt dilatert/utvidet for dette på sykehus
- 4.Ja, må jevnlig til dilatasjon/utvidelse på sykehus for dette

32. Har du krampeliggende smerter i endetarmen i forbindelse med avføring?

- 1.Aldri
- 2.Sjelden (en gang eller sjeldnere pr. måned)
- 3.Noen ganger (mer enn en gang pr. måned, men sjeldnere enn en gang pr. uke)
- 4.Ukentlig
- 5.Daglig

33. Har du smerter fra endetarmen/setet?

- 1.Aldri
- 2.Sjelden (en gang eller sjeldnere pr. måned)
- 3.Noen ganger (mer enn en gang pr. måned, men sjeldnere enn en gang pr. uke)
- 4.Ukentlig
- 5.Daglig

34. Har du magesmerter?

- 1.Aldri (Hvis aldri, gå videre til spørsmål 37)
- 2.Sjelden (en gang eller sjeldnere pr. måned)
- 3.Noen ganger (mer enn en gang pr. måned, men sjeldnere enn en gang pr. uke)
- 4.Ukentlig
- 5.Daglig

35. Tar du smertestillende medisiner på grunn av smerter fra mage eller endetarm?

- 1.Aldri (Hvis aldri, gå til spørsmål 37)
- 2.En gang i blant
- 3.Daglig
- 4.Er operert på grunn av smertene



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42. Hvor tilfreds er du med tarmfunksjonen din?

- 1.Svært fornøyd
- 2.Noe fornøyd
- 3.Nøytral
- 4.Noe misfornøyd
- 5.Svært misfornøyd

De neste spørsmålene vil handle om vannlatingsplager.
Vi er interessert i hvordan vannlatingen har vært den siste måneden.

43. Hvor lang tid er det mellom hver gang du må late vannet?

- 1.> 4 timer
- 2. 3-4 timer
- 3. 2-3 timer
- 4. 1-2 timer
- 5.Hver time

44. Har du dårlig trykk på urinstrålen?

- 1.Aldri
- 2. Månedlig
- 3. Ukentlig
- 4. Hver dag, bruker ikke kateter
- 5.Hver dag, bruker kateter

45. Har du svie eller smerter ved vannlating?

- 1.Aldri (Hvis aldri, gå til spørsmål 48)
- 2.Sjelden (en gang eller sjeldnere pr. måned)
- 3.Noen ganger (mer enn en gang pr. måned, men sjeldnere enn en gang pr. uke)
- 4.Ukentlig
- 5.Daglig

46. Bruker du smertestillende mot disse plagene?

- 1.Aldri (Hvis aldri, gå til spørsmål 48)
- 2.En gang i blant
- 3.Daglig
- 4.Er operert på grunn av smertene



Pasientnr:

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52. Medfører vannlatingsmønsteret ditt begrensinger i dagliglivets aktiviteter (f.eks. jobb, fritidsaktiviteter eller husarbeide)?

- 1.Store begrensinger
- 2.Noen begrensinger
- 3.Ingen begrensinger

53. Medfører vannlatingsmønsteret begrensinger i ditt sosiale liv?

- 1.Store begrensinger
- 2.Noen begrensinger
- 3.Ingen begrensinger

54. Hvor tilfreds er du med vannlatingsfunksjonen din?

- 1.Svært fornøyd
- 2.Noe fornøyd
- 3.Nøytral
- 4.Noe misfornøyd
- 5.Svært misfornøyd

De siste spørsmålene vil handle om hoftesmerter og røyking.

55. Har du smerter i hoften som du ikke hadde før behandlingen for endetarmskreft?

- 1.Aldri (Hvis nei, gå til spørsmål 58)
- 2.Sjelden (en gang eller sjeldnere pr. måned)
- 3.Noen ganger (mer enn en gang pr. måned, men sjeldnere enn en gang pr. uke)
- 4.Ukentlig
- 5.Daglig

56. Bruker du medisiner på grunn av hoftesmertene?

- 1.Aldri (Hvis aldri, gå til spørsmål 58)
- 2.En gang i blant
- 3.Daglig
- 4.Er operert på grunn av smertene



Appendix Ó



EORTC QLQ-C30 (version 3.0.)

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette en ring rundt det tallet som best beskriver din tilstand. Det er ingen "riktige" eller "gale" svar. Alle opplysningene vil bli behandlet konfidensielt.

Ditt navns forbokstaver:

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Født (dag, mnd, år):

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Dato (dag, mnd, år):

31

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	Ikke i det hele tatt	Litt	Endel	Svært mye
1. Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	1	2	3	4
2. Har du vanskeligheter med å gå en <u>lang</u> tur?	1	2	3	4
3. Har du vanskeligheter med å gå en <u>kort</u> tur utendørs?	1	2	3	4
4. Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	1	2	3	4
5. Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	1	2	3	4

I løpet av den siste uka:

	Ikke i det hele tatt	Litt	Endel	Svært mye
6. Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	1	2	3	4
7. Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	1	2	3	4
8. Har du vært tung i pusten?	1	2	3	4
9. Har du hatt smerter?	1	2	3	4
10. Har du hatt behov for å hvile?	1	2	3	4
11. Har du hatt søvnproblemer?	1	2	3	4
12. Har du følt deg slapp?	1	2	3	4
13. Har du hatt dårlig matlyst?	1	2	3	4
14. Har du vært kvalm?	1	2	3	4

Bla om til neste side

Appendix Ô

Senfølger etter behandling av kreft i endetarmen

Spørreskjema om seksualfunksjon, menn

Pasientnr:

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Fødselsår:

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Følgende spørsmål gjelder hvordan dine ereksjonsproblemer har virket inn på sexlivet ditt **i løpet av de siste 4 ukene.** Vennligst svar på spørsmålene så oppriktig og klart som mulig. Vennligst svar på hvert av spørsmålene ved å merke av én rute med et kryss [X]. Hvis du er usikker på hva du skal svare, svar så godt du kan.

Følgende definisjoner gjelder når du svarer på disse spørsmålene:

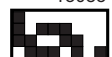
- * **Samleie**
Defineres som inntrenging (innføring) i partnerens skjede.
- ** **Seksuell aktivitet**
Omfatter samleie, kjærtegn, forspill og onani.
- *** **Sæduttømming**
Defineres som uttømming av sæd fra penis (eller fornemmelsen av dette).
- **** **Seksuell stimulering**
Omfatter slike situasjoner som erotisk lek med en partner, det å se på erotiske bilder, osv.

1. I løpet av de siste 4 ukene hvor ofte var du i stand til å få ereksjon under seksuell aktivitet ** ?
Vennligst kryss av i bare én rute.

- | | |
|--|--------------------------|
| 1. Ingen seksuell aktivitet | <input type="checkbox"/> |
| 2. Nesten alltid eller alltid | <input type="checkbox"/> |
| 3. De fleste gangene (mye mer enn halvparten av gangene) | <input type="checkbox"/> |
| 4. Ibland (omtrent halvparten av gangene) | <input type="checkbox"/> |
| 5. Noen få ganger (mye mindre enn halvparten av gangene) | <input type="checkbox"/> |
| 6. Nesten aldri eller aldri | <input type="checkbox"/> |

2. I løpet av de siste 4 ukene når fikk du ereksjon med seksuell stimulering ****, hvor ofte var ereksjonene stive nok til inntrenging?
Vennligst kryss av i bare én rute.

- | | |
|--|--------------------------|
| 1. Ingen seksuell stimulering | <input type="checkbox"/> |
| 2. Nesten alltid eller alltid | <input type="checkbox"/> |
| 3. De fleste gangene (mye mer enn halvparten av gangene) | <input type="checkbox"/> |
| 4. Ibland (omtrent halvparten av gangene) | <input type="checkbox"/> |
| 5. Noen få ganger (mye mindre enn halvparten av gangene) | <input type="checkbox"/> |
| 6. Nesten aldri eller aldri | <input type="checkbox"/> |



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De 3 neste spørsmålene gjelder de ereksjonene du eventuelt har hatt under samleie*.

3. I løpet av de siste 4 ukene når du forsøkte å ha samleie*, hvor ofte var du i stand til å trenge inn i partneren?

Vennligst kryss av i bare én rute.

- | | |
|--|--------------------------|
| 1. Har ikke forsøkt å ha samleie | <input type="checkbox"/> |
| 2. Nesten alltid eller alltid | <input type="checkbox"/> |
| 3. De fleste gangene (mye mer enn halvparten av gangene) | <input type="checkbox"/> |
| 4. Iblant (omtrent halvparten av gangene) | <input type="checkbox"/> |
| 5. Noen få ganger (mye mindre enn halvparten av gangene) | <input type="checkbox"/> |
| 6. Nesten aldri eller aldri | <input type="checkbox"/> |

4. I løpet av de siste 4 ukene under samleie* **hvor ofte** var du i stand til å beholde ereksjonen etter inntrenging i partneren?

Vennligst kryss av i bare én rute.

- | | |
|--|--------------------------|
| 1. Har ikke forsøkt å ha samleie | <input type="checkbox"/> |
| 2. Nesten alltid eller alltid | <input type="checkbox"/> |
| 3. De fleste gangene (mye mer enn halvparten av gangene) | <input type="checkbox"/> |
| 4. Iblant (omtrent halvparten av gangene) | <input type="checkbox"/> |
| 5. Noen få ganger (mye mindre enn halvparten av gangene) | <input type="checkbox"/> |
| 6. Nesten aldri eller aldri | <input type="checkbox"/> |

5. I løpet av de siste 4 ukene under samleie* **hvor vanskelig** var det å beholde ereksjonen til samleiet var fullført?

Vennligst kryss av i bare én rute.

- | | |
|----------------------------------|--------------------------|
| 1. Har ikke forsøkt å ha samleie | <input type="checkbox"/> |
| 2. Ekstremt vanskelig | <input type="checkbox"/> |
| 3. Svært vanskelig | <input type="checkbox"/> |
| 4. Vanskelig | <input type="checkbox"/> |
| 5. Litt vanskelig | <input type="checkbox"/> |
| 6. Ikke vanskelig | <input type="checkbox"/> |

* **Samleie:** Defineres som inntrenging (innføring) i partnerens skjede.

** **Seksuell aktivitet:** Omfatter samleie, kjærtegn, forspill og onani.

*** **Sæduttømming:** Defineres som uttømming av sæd fra penis (eller fornemmelsen av dette).

**** **Seksuell stimulering:** Omfatter slike situasjoner som erotisk lek med en partner, det å se på erotiske bilder, osv.



6. I løpet av de siste 4 ukene hvor mange ganger har du forsøkt å ha samleie*?

Vennligst kryss av i bare én rute.

- 1. Ingen forsøk
- 2. 1-2 forsøk
- 3. 3-4 forsøk
- 4. 5-6 forsøk
- 5. 7-10 forsøk
- 6. 11 eller flere forsøk

7. I løpet av de siste 4 ukene når du forsøkte å ha samleie*, hvor ofte var det tilfredsstillende for deg?

Vennligst kryss av i bare én rute.

- 1. Har ikke forsøkt å ha samleie
- 2. Nesten alltid eller alltid
- 3. De fleste gangene (mye mer enn halvparten av gangene)
- 4. Iblant (omtrent halvparten av gangene)
- 5. Noen få ganger (mye mindre enn halvparten av gangene)
- 6. Nesten aldri eller aldri

8. I løpet av de siste 4 ukene hvor mye glede har du hatt av samleie*?

Vennligst kryss av i bare én rute.

- 1. Ikke samleie
- 2. Svært mye glede
- 3. Mye glede
- 4. En del glede
- 5. Lite glede
- 6. Ingen glede

* **Samleie:** Defineres som inntrenging (innføring) i partnerens skjede.

** **Seksuell aktivitet:** Omfatter samleie, kjærtegn, forspill og onani.

*** **Sæduttømming:** Defineres som uttømming av sæd fra penis (eller fornemmelsen av dette).

**** **Seksuell stimulering:** Omfatter slike situasjoner som erotisk lek med en partner, det å se på erotiske bilder, osv.



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9. I løpet av de siste 4 ukene under seksuell stimulering ****, eller samleie *,
 hvor ofte hadde du sæduttømming?

Vennligst kryss av i bare én rute.

- | | |
|--|--------------------------|
| 1. Ingen seksuell stimulering eller samleie | <input type="checkbox"/> |
| 2. Nesten alltid eller alltid | <input type="checkbox"/> |
| 3. De fleste gangene (mye mer enn halvparten av gangene) | <input type="checkbox"/> |
| 4. Ibland (omtrent halvparten av gangene) | <input type="checkbox"/> |
| 5. Noen få ganger (mye mindre enn halvparten av gangene) | <input type="checkbox"/> |
| 6. Nesten aldri eller aldri | <input type="checkbox"/> |

10. I løpet av de siste 4 ukene under seksuell stimulering ****, eller samleie *,
 hvor ofte hadde du følelsen av orgasme med eller uten sæduttømming *** ?

Vennligst kryss av i bare én rute.

- | | |
|--|--------------------------|
| 1. Ingen seksuell stimulering eller samleie | <input type="checkbox"/> |
| 2. Nesten alltid eller alltid | <input type="checkbox"/> |
| 3. De fleste gangene (mye mer enn halvparten av gangene) | <input type="checkbox"/> |
| 4. Ibland (omtrent halvparten av gangene) | <input type="checkbox"/> |
| 5. Noen få ganger (mye mindre enn halvparten av gangene) | <input type="checkbox"/> |
| 6. Nesten aldri eller aldri | <input type="checkbox"/> |

11. I løpet av de siste 4 ukene under seksuell stimulering ****, eller samleie *,
 hvor ofte hadde du følelsen av orgasme, men uten sæduttømming *** ?

Vennligst kryss av i bare én rute.

- | | |
|--|--------------------------|
| 1. Ingen seksuell stimulering eller samleie | <input type="checkbox"/> |
| 2. Nesten alltid eller alltid | <input type="checkbox"/> |
| 3. De fleste gangene (mye mer enn halvparten av gangene) | <input type="checkbox"/> |
| 4. Ibland (omtrent halvparten av gangene) | <input type="checkbox"/> |
| 5. Noen få ganger (mye mindre enn halvparten av gangene) | <input type="checkbox"/> |
| 6. Nesten aldri eller aldri | <input type="checkbox"/> |

- * **Samleie:** Defineres som inntrenging (innføring) i partnerens skjede.
- ** **Seksuell aktivitet:** Omfatter samleie, kjærtegn, forspill og onani.
- *** **Sæduttømming:** Defineres som uttømming av sæd fra penis (eller fornemmelsen av dette).
- **** **Seksuell stimulering:** Omfatter slike situasjoner som erotisk lek med en partner, det å se på erotiske bilder, osv.



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De 2 neste spørsmålene gjelder seksuelt begjær. La oss definere seksuelt begjær som en følelse som kan omfatte et ønske om å ha en seksuell opplevelse (f.eks. onani eller samleie *), å tenke på sex eller å være frustrert over mangel på sex.

12. I løpet av de siste 4 ukene hvor ofte har du følt **seksuelt begjær**?

Vennligst kryss av i bare én rute.

- | | |
|-----------------------------------|--------------------------|
| 1.Nesten alltid eller alltid | <input type="checkbox"/> |
| 2.Svært ofte (svært mye av tiden) | <input type="checkbox"/> |
| 3.Av og til (en del av tiden) | <input type="checkbox"/> |
| 4.Sjelden (litt av tiden) | <input type="checkbox"/> |
| 5.Nesten aldri eller aldri | <input type="checkbox"/> |

13. I løpet av de siste 4 ukene hvordan vil du beskrive nivået på ditt **seksuelle begjær**?

Vennligst kryss av i bare én rute.

- | | |
|--------------------------|--------------------------|
| 1.Svært høyt | <input type="checkbox"/> |
| 2.Høyt | <input type="checkbox"/> |
| 3.Middels | <input type="checkbox"/> |
| 4.Lavt | <input type="checkbox"/> |
| 5.Svært lavt eller intet | <input type="checkbox"/> |

14. I løpet av de siste 4 ukene hvor tilfreds har du vært med **sexlivet** ditt alt i alt?

Vennligst kryss av i bare én rute.

- | | |
|---|--------------------------|
| 1.Svært tilfreds | <input type="checkbox"/> |
| 2.Ganske tilfreds | <input type="checkbox"/> |
| 3.Omtrent like mye tilfreds som utilfreds | <input type="checkbox"/> |
| 4.Ganske utilfreds | <input type="checkbox"/> |
| 5.Svært utilfreds | <input type="checkbox"/> |

- * **Samleie:** Defineres som inntrenging (innføring) i partnerens skjede.
- ** **Seksuell aktivitet:** Omfatter samleie, kjærtegn, forspill og onani.
- *** **Sæduttømming:** Defineres som uttømming av sæd fra penis (eller fornemmelsen av dette).
- **** **Seksuell stimulering:** Omfatter slike situasjoner som erotisk lek med en partner, det å se på erotiske bilder, osv.



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15. I løpet av de siste 4 ukene hvor tilfreds har du vært med ditt **seksuelle forhold** til din partner?

Vennligst kryss av i bare én rute.

- | | |
|---|--------------------------|
| 1.Svært tilfreds | <input type="checkbox"/> |
| 2.Ganske tilfreds | <input type="checkbox"/> |
| 3.Omtrent like mye tilfreds som utilfreds | <input type="checkbox"/> |
| 4.Ganske utilfreds | <input type="checkbox"/> |
| 5.Svært utilfreds | <input type="checkbox"/> |

16. I løpet av de siste 4 ukene hvordan vil du beskrive din **tiltro** til å kunne få og beholde en ereksjon

Vennligst kryss av i bare én rute.

- | | |
|---------------|--------------------------|
| 1.Svært stor | <input type="checkbox"/> |
| 2.Stor | <input type="checkbox"/> |
| 3.Middels | <input type="checkbox"/> |
| 4.Liten | <input type="checkbox"/> |
| 5.Svært liten | <input type="checkbox"/> |

17. I løpet av de siste 4 ukene har du brukt medikamenter eller hjelpemidler (tabletter, sprøyter, implantat) for å oppnå ereksjon?

1. Nei 2. Ja Hvilke?

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* **Samleie:** Defineres som inntrenging (innføring) i partnerens skjede.
 ** **Seksuell aktivitet:** Omfatter samleie, kjærtegn, forspill og onani.
 *** **Sæduttømming:** Defineres som uttømming av sæd fra penis (eller fornemmelsen av dette).
 **** **Seksuell stimulering:** Omfatter slike situasjoner som erotisk lek med en partner, det å se på erotiske bilder, osv.

Appendix Ö

Senfølger etter behandling av kreft i endetarmen

Spørreskjema om seksualfunksjon, kvinner

Pasientnr:

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Fødselsår:

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Fysisk kontakt og seksuelt samvær kan være en viktig del av mange menneskers liv.

Personer som får sykdommer som involverer underlivet, kan oppleve endringer i seksuallivet.

De følgende spørsmål handler om dette.

Svarene vil bli behandlet streng fortrolig.

Vennligst svar på alle spørsmålene selv ved å sette et kryss i den ruten som best beskriver din tilstand.

Del 1. I løpet av den siste måneden:	Ikke i det hele tatt	Litt	En del	Svært mye	
1. Har du hatt ønske om nær fysisk kontakt (klem og kyss)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2. Har du hatt nær fysisk kontakt med dine nærmeste?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
3. Har du hatt ønske om seksuelt samvær?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	Ja	Nei			
4. Har du en partner? (Hvis ikke, vennligst fortsett til spørsmål 8).	<input type="checkbox"/>	<input type="checkbox"/>			
5. Har din partner hatt ønske om seksuelt samvær?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	Nei	Ja, 1-2 ganger i måneden	Ja, 3-4 ganger i måneden	Ja, 1-2 ganger i uken	Ja, mer enn 2 ganger i uken
6. Har dere hatt seksuelt samvær? (Hvis du har svart "nei" til dette spørsmålet, vennligst fortsett til spørsmål 8).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Ikke i det hele tatt	Litt	En del	Svært mye	
7. Hadde din partner problemer med å få ereksjon?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
8. Har ditt seksualliv/mangel på seksualliv gitt deg bekymringer?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Bla om til neste side



