From DEPARTMENT OF MOLECULAR MEDICINE AND SURGERY

Karolinska Institutet, Stockholm, Sweden

ADVERSE EFFECTS OF TREATMENT FOR RECTAL CANCER

SEXUAL FUNCTION, HORMONES, AND BONE HEALTH

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Stockholm 2022

Published by Karolinska Institutet.

Printed by Universitetsservice US-AB, 2022

ISBN 978-91 -8016-340-8

Adverse effects of treatment for rectal cancer

Sexual function, hormones, and bone health

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public at Capio S:t Göran's Hospital, Stockholm
November 11, 2022, 09.00 a.m.

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LIST OF SCIENTIFIC PAPERS

I. **Effect of radiotherapy for rectal cancer on ovarian androgen production**
Segelman J, Buchli C, Svanström Röjvall A, Matthiessen P, Arver S, Bottai M, Ahlberg M, Jasuja R, Flöter-Rådestad A, Martling A.
Br J Surg. 2019 Feb;106(3):267-275. doi: 10.1002/bjs.10980. Epub 2018 Sep 12. PMID: 30277569

II. **Effect of radiotherapy for rectal cancer on female sexual function: a prospective cohort study**
Svanström Röjvall A, Buchli C, Bottai M, Ahlberg M, Flöter-Rådestad A, Martling A, Segelman J.
Br J Surg. 2020 Apr;107(5):525-536. doi: 10.1002/bjs.11373. Epub 2019 Dec 3. PMID: 31792944

III. **Impact of androgens on sexual function in women with rectal cancer – a prospective cohort study**
Svanström Röjvall A, Buchli C, Flöter Rådestad A, Martling A, Segelman J, *J Sex Med*. 2021 Aug;18(8):1374-1382.
doi: 10.1016/j.jsxm.2021.05.018. Epub 2021 Jul 18.PMID: 34284953

IV. **Impact of radiotherapy on bone health in women with rectal cancer – A prospective cohort study**
Svanström Röjvall A, Buchli C, Sääf M, Magnusson P, Flöter Rådestad A, Martling A, Segelman J, *Eur J Surg Oncol.*
Epub 2022 Jun 23; S0748-7983(22)00533-9.
doi: 10.1016/j.ejso.2022.06.028. PMID: 35786532

V. **Addressing sexual side effects from rectal cancer treatment – a study among physicians and patients**
Svanström Röjvall A, Sjövall A, Martling A, Flöter Rådestad A, Buchli C, Segelman J, *Manuscript*

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LIST OF ABBREVIATIONS

A-4	Androstenedione
AMH	Anti-Müllerian Hormone
BALP	Bone specific alkaline phosphatase
BMD	Bone Mineral Density
BMI	Body Mass Index
BTM	Bone Turnover Marker
CAPOX	Capecitabin and Oxaliplatin
CR	Complete response
CRC	Colorectal cancer
CRT	Chemoradiotherapy
(C)RT	(Chemo)radiotherapy, used for radiotherapy with or without chemotherapy
cTNM	Clinical TNM
CTVN	Clinical Target Volume – Nodal
CTVT	Clinical Target Volume – Tumour
DFS	Disease-free survival
CT	Computed Tomography
CTX-1	Carboxy-terminal crosslinking telopeptide of type 1 collagen
DHEAS	Dehydroepiandrosterone Sulfate
EORTC-QLQ	European Organisation for Research and Treatment of Cancer's Quality of Life Questionnaire
FLv	Bolus 5-fluorouracil and Folinic acid
5-FU	5-fluorouracil
FSD	Female Sexual Dysfunction
FSH	Follicular-Stimulating Hormone
FOLFOX	Folinic acid, 5-FU, and oxaliplatin
FOLFOXIRI	FOLFOX and irinotecan
GTV	Gross Tumour Volume
GTVT	Gross Tumour Volume – Tumour
FSFI	Female Sexual Function Index
Gy	Gray (1Gy = 1 Joule /kg)
HR	Hazard Ratio
LH	Luteinising Hormone
MDC	Multidisciplinary Conference
MRI	Magnetic Resonance Imaging

MSI	Microsatellite Instability
OS	Overall survival
pCR	Pathological Complete response
PGWBI	Psychological General Well-being Index
PIF	Pelvic Insufficiency Fracture
PINP	Amino-terminal propeptide of type I procollagen
pTNM	Pathological TNM
RC	Rectal cancer
RCSF	Rectal Cancer Sexual Function
RT	Radiotherapy
SCRT	Short-Course Radiotherapy
SHBG	Sex Hormone-Binding Globulin
SVQ	Sexual Function-Vaginal changes Questionnaire
T	Testosterone
TME	Total Mesorectal Excision
TNM	Tumour Nodes Metastases

1 ABSTRACT

Thanks to improved outcomes from multimodal rectal cancer (RC) treatment, long-term survival is increasing; thus, focus on the long-term adverse effects of treatment is required. This thesis aimed to increase knowledge regarding adverse effects to enable well-informed treatment decisions and accurate management of the side effects. Studies I–IV were part of a multicentre, prospective cohort study including 142 females with RC stage I–III from 2008 to 2013. Clinical data and blood samples for hormone and bone biomarker analysis were collected at baseline, after (chemo)radiotherapy (C)RT, and at one year. Questionnaires on sexual function (Female Sexual Function Index; FSFI) and psychological well-being were completed at baseline and one- and two-year follow-up, and on bowel function at two years.

Female androgens are produced in the ovaries, adrenals and by peripheral conversion. **Study I** explored the impact of preoperative RT on ovarian androgen production and the association between androgens and sexual desire. Testosterone (T), free T, androstenedione (A-4), and dehydroepiandrosterone sulfate (DHEAS) were assessed and compared between non-oophorectomized females treated with RT and surgery (RT+) vs surgery alone (RT-) (N=125). Radiotherapy was associated with a decrease in the androgens predominantly produced in the ovaries (T and free T). Changes in serum levels of all measured androgens were associated with sexual desire.

Rectal cancer treatment negatively affects sexual function, with data being more robust for males than females. **Study II** aimed to assess sexual function and its association with RT in females. The FSFI scores were assessed in all women who completed the questionnaire at least once during the two years follow-up (N=139). Total and domain scores were compared within and between the treatment groups (RT+ *vs* RT-), and the associations between RT and change in FSFI scores were explored in multivariable models. Radiotherapy was associated with a decline in FSFI total score and the domain scores of arousal, lubrication, orgasm, and pain. A secondary aim was to assess ovarian reserve. Anti-Müllerian hormone was measured in premenopausal females (N=9) and became undetectable after RT.

Data indicate that androgens are important for female sexual function. The role of endogenous androgen levels in sexual function was not previously investigated in females with RC. **Study III** explored the association between endogenous levels of the four androgens specified above and FSFI scores among sexually active females (N=99). Increasing levels of T and A-4 were associated with increased FSFI total score, and at least any of T, free T, and A-4 were associated with the FSFI domains of sexual arousal, lubrication, orgasm, or pain.

Pelvic insufficiency fractures are a complication of RT for RC. Serum bone biomarkers reflecting the bone remodelling process have been suggested as useful in assessing bone health. **Study IV** assessed four bone biomarkers in 134 participants, explored their changes after RC treatment, and if the changes were associated with RT. The prevalence of bone damage was evaluated in a subgroup with magnetic resonance imaging (N=41). Two bone formation markers increased significantly in the RT group between baseline and one year. In the multivariable analysis, RT was associated with an increased level of one of these markers. Bone damage was present in 16 of 38 females who had RT in the subgroup.

Study V investigated if patients were given information regarding sexual side effects. Two surveys were directed at physicians and RC patients, respectively; the numbers participating were 186 and 253. Among physicians, approximately half reported that they addressed sexual side effects before

treatment, with more than half of the patients and more males than females. Almost half of the patients recalled getting information before treatment. High age, poor physical status among patients, and short clinical experience among physicians decreased the odds of information being provided.

In conclusion, the results indicate that RT negatively affects sexual function, androgens, and bone health and show room for improvement in the pre-treatment information about and follow-up of sexual side effects with patients.

2 POPULAR SCIENCE SUMMARY IN SWEDISH

Behandling av rektalcancer (ändtarmscancer) har utvecklats mycket under de senaste decennierna vilket lett till minskade återfall lokalt i bäckenet och förbättrad överlevnad. Standardbehandling för rektalcancer utan spridning till andra organ är operation med eller utan föregående strålbehandling, ibland kombinerat med cellgiftsbehandling. Den förbättrade överlevnaden innebär att långtidsbiverkningar blir viktigare att ta hänsyn till i forskning och klinik. Som patient har man rätt att få information om både förväntad nytta och förväntade risker med planerad behandling. Det är en förutsättning för att kunna fatta ett välgrundat behandlingsbeslut och för att biverkningar ska uppmärksammas och kunna åtgärdas om de uppstår. Avhandlingen syftar till att öka kunskapen hos vårdgivare och patienter angående långtidsbiverkningar från rektalcancerbehandling. Fokus ligger framförallt på strålbehandlingens eventuella påverkan på sexuell funktion, könshormoner (androgener) och skelettets kvalitet hos kvinnor. Avhandlingen undersöker också i vilken utsträckning patienter får information angående risken för sexuella biverkningar och fertilitet.

Studie I syftade till att ta reda på om androgennivåer hos kvinnor påverkas av behandlingen och om detta i så fall har ett samband med given strålbehandling. En hypotes var att äggstockarnas androgenproduktion kunde påverkas negativt av strålbehandlingen p.g.a. att äggstockarna omfattas av strålfältet. Fyra androgener mättes före start av behandling, efter strålbehandling och ett år efter operation. Förändring av androgennivåer jämfördes mellan strålbehandlade och ej strålbehandlade kvinnor. Analysen påvisade samband mellan given strålbehandling och minskning av androgenerna testosteron och fritt testosteron, som till stor del produceras i äggstockarna. Det fanns också ett samband mellan förändring av alla androgennivåer och sexuell lust.

Studie II jämförde sexuell funktion mellan strålbehandlade och ej strålbehandlade kvinnor. Dessutom undersöktes påverkan på fertilitet genom mätning av anti-Mülleriskt hormon. Sexuell funktion mättes med självskattningsformuläret Female Sexual Function Index (FSFI) som ger ett totalvärde och separata värden för ingående domäner: sexuell lust, upphetsning, lubrikation, orgasm, smärta vid samlag och tillfredställelse med sexlivet. Formuläret fylldes i före behandling och efter ett och två år. Alla FSFI-värden sjönk i den strålbehandlade gruppen medan alla värden utom ett var oförändrade i den ej strålbehandlade gruppen. Fertilitetshormonet var omätbart efter strålbehandling hos det fåtal patienter som vid studiestart hade mätbara värden. Sammanfattningsvis visade studien att strålbehandling bidrar till försämrat sexliv och de uppmätta värdena av Anti-Mülleriskt hormon avspeglade infertilitet.

Studie III undersökte samband mellan androgennivåer och sexuell funktion mätt med FSFI hos endast sexuellt aktiva kvinnor. Hypotesen var att minskade androgennivåer skulle kunna påverka sexuell funktion negativt. Det är inte tydligt visat att de kroppsegna

androgennivåerna hos kvinnor har betydelse för sexuell funktion även om ett flertal studier tyder på det. Resultaten visade ett samband mellan de två androgenerna testosteron och androstendion och sexuell funktion. Detta tyder på att androgener kan ha betydelse för sexualfunktionen hos kvinnor med rektalcancer trots att det i denna grupp finns många andra möjliga faktorer som kan påverka funktionen negativt. Resultaten kan vara till nytta för framtida studier angående behandling av sexuella problem efter rektalcancerbehandling men detta behöver studeras mer för säkrare resultat.

Studie IV syftade till att ta reda på om skelettmarkörer, som mäts i blodet, förändras efter rektalcancerbehandling och om detta i så fall har ett samband med strålbehandling. Det är känt att strålbehandling av cancer i bäckenet kan ge försämrad benhälsa och frakturer i bäckenskelettet. Skelettmarkörer kan avspegla den nedbrytning och uppbyggnad av skelettet som sker kontinuerligt för att hålla skelettet friskt och hållfast. I dagsläget används skelettmarkörer framförallt vid behandling av benskörhet. I studie IV kontrollerades fyra markörer i blodprover tagna före behandling, efter strålbehandling och efter ett år. Båda markörerna som avspeglar uppbyggnad av skelettet tenderade att först minska lätt i den strålbehandlade gruppen och sedan öka till ett-årsuppföljningen. Ökningen skulle kunna avspegla en reparationsfas efter strålskador i skelettet, vilka var vanligt förekommande i den subgrupp som undersöktes för detta. Inga slutsatser kunde dras angående samband mellan frakturer och benmarkörer. Resultaten kan ligga till grund för mer omfattande studier på området.

Studie V undersökte i vilken utsträckning patienter får information om risk för sexuella biverkningar och påverkan på fertilitet. Fokus i studien låg på information inför behandling som ges i botande syfte men frågorna täckte också in information och råd efter behandling och (i läkarenkäten) vid icke botbar sjukdom. Läkare och patienter tillfrågades via olika enkäter och vid olika tidpunkter och svaren analyserades separat. Ungefär hälften av läkarna uppgav att de informerade patienter om sexuella biverkningar inför behandling. Längre yrkeserfarenhet ökade sannolikheten att ämnet togs upp. Läkarna informerade män i högre utsträckning än kvinnor. Orsaker till att avstå från att informera var bland annat hög ålder och sjuklighet hos patienten och att ämnet inte prioriterades. Bland patienterna uppgav knappt hälften av både män och kvinnor att de fick information inför behandling. Även här framkom att ökande ålder och sjuklighet minskade sannolikheten att få information. Studien visade bristfällig kunskap bland läkare om sexuella biverkningar samt hantering av dessa. Sammanfattningsvis framkom behov av vidareutbildning inom området.

3 BACKGROUND

3.1 RECTAL CANCER EPIDEMIOLOGY AND AETIOLOGY

Colorectal cancer (CRC) is the third most common cancer worldwide, after breast and lung cancer, and the second most common cause of cancer-related death (5, 6). The incidence varies between countries and regions and is highest in Europe, North America, Australia and East Asia (7). Age is an important risk factor, but cannot explain the wide geographic incidence gap. Instead, these differences appear to be attributed to lifestyle factors; the risk of developing the disease clearly increases with aspects of the lifestyle in developed countries including dietary patterns with high intake of red and processed meat and low intake of fibres and vegetables. Healthy dietary patterns, high physical activity, normal weight and waist circumference, non-smoking and limited alcohol consumption are protective (8-15).

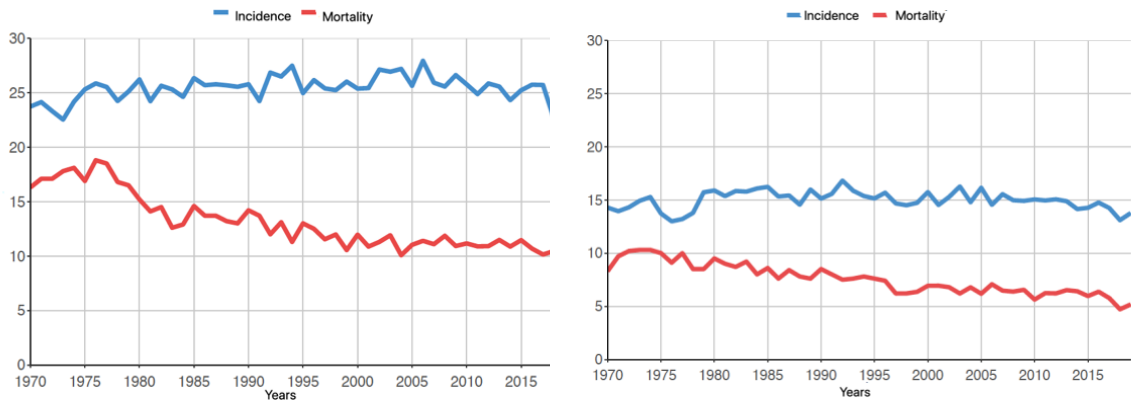

Figure 1. Y-axis: Age-standardised incidence and mortality in Swedish males (left) and females (right) per 100 000 inhabitants, 1970–2019.

Hereditary forms with moderate or high cancer risk account for about 6–10% of all CRC cases and a higher proportion of early-onset CRC (16). The most commonly occurring, Lynch Syndrome or Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is caused by germline mutations in either of the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, or *PMS2*, or the *EPCAM* gene. A deficient MMR causes microsatellite instability (MSI), resulting in a high mutational burden and an increased cancer risk. These tumours show a decreased sensitivity to standard chemotherapy and may respond well to immunotherapy at a group level. Among the polyposis-forming syndromes, the Familial Adenomatous Polyposis (FAP), caused by germline mutations in the *APC*-gene, is of most clinical importance, although uncommon (1%) (16). There is a considerable risk of malignant transformation of the numerous polyps present in FAP if prophylactic surgery is not performed.

In Sweden, CRC is the second most common cancer among both males and females following prostate and breast cancer, respectively, when excluding skin tumours other than

melanoma. Rectal cancer (RC) accounts for approximately one third of cases (17). The yearly incidence of RC in females and males was 19.2/100,000 and 27.7/100,000, respectively, in 2019, and the age-adjusted incidence in the total population has been stable with only small fluctuations during the last 15–20 years (*Fig. 1*(2)), while RC in males and females < 50 years has increased (18, 19). A total of 2,406 new cases of RC were registered in 2019, of which 980 were in females and 1,426 in males. The median overall survival (OS) was 66% five years post-diagnosis in both sexes and 61% and 57% in females and males, respectively, after ten years (17), differing with disease stage at diagnosis (*Fig. 2*).

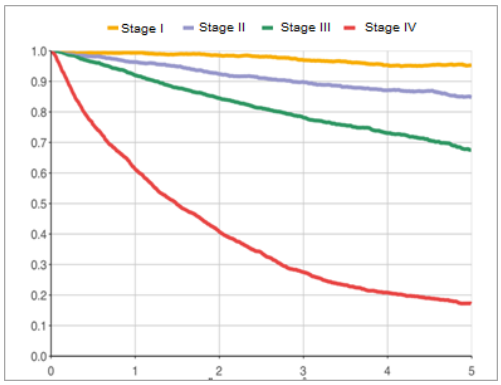

Figure 2. (2)
Y-axis: Relative survival depending on disease stage at diagnosis. X-axis: Survival time (years).

As a result of previous studies performed by international and Swedish research groups, standard treatment for RC stage I–III is now surgical resection with or without preoperative (chemo)radiotherapy ((C)RT), and adjuvant chemotherapy in selected patients (20-25). In the era before modern surgery, the Stockholm I and II trials demonstrated that the addition of short-course preoperative RT reduced the local recurrence rates by half (20, 21). Modern surgery with total mesorectal excision (TME) (26) increased survival and led to dramatical improvements in local recurrence rates (*Fig. 3*) (22, 25, 27-29).

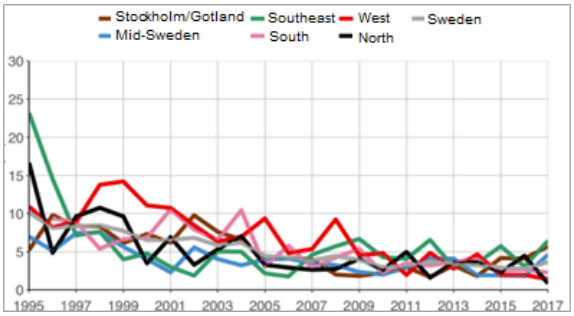

Figure 3. Local recurrence rates (y-axis) in different parts of Sweden decreasing and becoming more homogenous over time (2).

Further improvements in disease control were achieved by combining modern surgery with preoperative (C)RT and by implementing a structured management of RC, including improved diagnostics and taking treatment decisions at multidisciplinary conferences (MDCs) (23, 24, 30, 31). The exact contribution of preoperative (C)RT to TME surgery is debated, the most important information source being the TME trial (24). According to a Cochrane review from 2018, preoperative (C)RT reduces local recurrences by half from an

already low level after surgery alone (32). In the Stockholm III trial, the local recurrence rates were 2.3–5.5%, depending on RT fractionation and timing of surgery (33).

The clinical tumour-nodes-metastasis (cTNM) stage (Table 1 (34, 35)), based on radiological findings from Magnetic Resonance Imaging (MRI) of the pelvis and computed tomography (CT) scan of the thorax and abdomen, is currently the most important prognostic factor guiding treatment decisions. At the preoperative MDC, other variables taken into account include tumour distance from the anal verge (assessed with rigid endoscopy), presence of extramural vascular invasion or threatened mesorectal fascia, and the patient's general condition, comorbidities, and opinions.

Table 1 TNM classification of CRC according to the UICC 8th edition

TNM stage	Tumour stage Tis–T4	Nodal stage N0–N2	Metastasis stage M0, M1
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage II A–C	T3, T4	N0	M0
Stage III A–C	Any T	N1, N2	M0
Stage IV A–C	Any T	Any N	M1 a–c

Tumour stage: Local invasion	
T0	No signs of primary tumour present.
Tis	Carcinoma *in situ*: Intra epithelial growth or invasion of lamina propria. No invasion into muscularis mucosae.
T1	Invasion into submucosa. Sm1–3: growth into 1/3, 2/3, and 3/3 of submucosa.
T2	Invasion into muscularis propria
T3	Invasion beyond muscularis propria into pericolorectal tissue. Depth of invasion (mm): T3a: < 1, T3b: 1–5, T3c: 6–15, T3d: > 15
T4	Invasion into surrounding organs or structures. T4a visceral peritoneum; T4b other organs or structures
Nodal stage: Loco-regional lymph node metastases or tumour deposits	
N0	No of lymph node metastases.
N1	< 4 (N1a: 1, N1b: 2–3, N1c: tumour deposits present)
N2	≥ 4 (N2a: 4–6, N2b: ≥ 7)
Metastasis stage: Distant metastases	
M0	No distant metastases.
M1	Distant metastases present. M1a: 1 organ including distant lymph nodes involved without peritoneal metastases. M1b: ≥ 1 organ involved. M1c: Peritoneal metastases with or without other organs involved.
Additional prefix are added to indicate the type of classification: c: clinical (MRI), p: histopathological yc: clinical TNM after preoperative radiotherapy and/or chemotherapy, yp: histopathological TNM after preoperative radiotherapy and/or chemotherapy, r: TNM in recurrent disease. Adopted from Amin 2017 (31, 32)	

Factors that, together with the pathological (p) TNM, will guide postoperative decisions on adjuvant treatment and follow-up are: histopathological information on resection margins, affected blood and lymph vessels and nerves, presence of tumour deposits, tumour differentiation grade (high/low), presence of bowel obstruction at diagnosis or tumour perforation, MSI status, and mutational status of the *DPYD* (dehydropyrimindine dehydrogenase) gene, which is essential for metabolism of the backbone drugs in (neo)adjuvant chemotherapy, 5-flourouracil (5-FU) or capecitabine. Information on MSI

and *DPYD* are likewise essential in the preoperative treatment decisions if chemotherapy is discussed.

3.2 RECTAL CANCER TREATMENT

The various and complex multimodal treatment strategies have led to the routine of discussing RC patients in MDCs. Surgeons, oncologists, radiologists, pathologists and specialised nurses meet to determine the optimal treatment recommendations for each patient and assess eligibility for clinical studies. Tumour characteristics and the patient's comorbidities, functional status and opinions are taken into account. The routine of discussing CRC at MDCs has proved to influence treatment decisions and seems to improve oncological outcomes primarily in advanced disease stages, although strong evidence is lacking (36-43).

3.2.1 Surgery

The gold standard surgical technique for RC is TME, developed by Heald in the 1980s (26). In this procedure, the resection line follows the mesorectal fascia so that mesorectal fat, with possible local tumour spread, is removed en bloc with the rectum. The introduction of the TME technique dramatically decreased local recurrence rates (25, 27, 28). A partial mesorectal excision (PME) is appropriate for early cancers in the very upper part of the rectum, if a distal tumour margin of at least five centimetres can be achieved (44). When the tumour is located in the upper or middle part of the rectum, a sphincter-sparing anterior resection (AR) with a colorectal anastomosis is the first choice of surgical method. A concomitant formation of a temporary diverting loop ileostomy minimises the risk of anastomotic leakage (45, 46). A stoma closure is usually performed within 3–6 months (47). An alternative to AR is Hartmann's procedure, used when a bowel anastomosis is inappropriate due to expected poor functional results after AR or high risk of anastomotic leakage. The rectum is divided and closed with a margin below the tumour without sphincter resection, and a permanent colostomy is established. This procedure may be associated with pelvic abscesses in the remaining anorectal stump, but data are conflicting (45, 48, 49). A perineal dissection with complete resection of the rectal stump, including the internal anal sphincter (inter-sphincteric abdominoperineal excision (APE)), may be preferred.

For tumours located in the distal part of the rectum, conventional or even more extensive forms of APE are often necessary to ensure an adequate tumour margin (50). The anus and anal canal are resected and a permanent colostomy performed. Conventional APE implies resection of the total sphincter complex and is recommended for low T1–T2 tumours.

When tumours are locally advanced, the risk of non-radical resection margins (CRM) and subsequent local recurrence is high. Therefore, the *levator ani* muscle, with or without the ischio-anal compartment, are resected from below, en bloc with the anal canal and rectum (extra levator APE (ELAPE) and ischio-anal APE, respectively) (51, 52).

In patients with T4b tumours with overgrowth to other pelvic organs or tissues, resection of the affected structures is necessary. In females, en bloc hysterectomy, oophorectomy and a complete or partial resection of the vagina may be performed. As ELAPE leaves a larger defect of the pelvic floor, primary closure of the surgical wound is not possible and a reconstruction with a mesh or flap is required (52-55). Delayed perineal wound healing is a common problem after APE, in particular after RT (52-57).

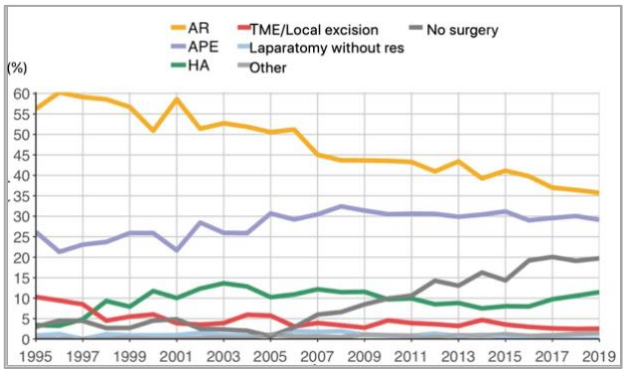

Figure 4.
Type of surgery used in patients without distant metastases (2).

The Swedish RC registry shows a change in surgical strategies over time, where the use of AR decreased for two decades (*Fig. 4*) (2), along with a growing awareness of the poor bowel function associated with AR (2). Instead, there is an increasing proportion of patients undergoing APE. The proportion of sphincter-preserving surgery varies between countries and is, e.g., higher in Denmark and the Netherlands than in Sweden (58, 59).

3.2.2 Radiotherapy

Type of irradiation and tumour biology

External irradiation with photons (gamma rays) is standard in preoperative treatment of RC. Photons gradually deposit energy as they pass through the body and interact with tissue or water molecules. The deposited energy is scattered in the close surroundings through a chain of chemical reactions, starting with ejection of electrons from their orbits and resulting in ionised molecules and highly damaging free radicals. The density of energy deposition varies with irradiation source, energy of the emitted particle, and the medium through which it passes. The cells suffer from primarily sublethal single strand breaks in the DNA and, to a lesser extent, more lethal double strand breaks. In well-oxygenated microenvironments, the damage from free radicals increases due to chemical reactions causing DNA strand breaks to become irreparable (60).

DNA damage in normal tissue triggers cells to protect DNA integrity to avoid cell death through apoptosis (programmed cell death), necrosis or the more commonly occurring mitotic catastrophe during dysfunctional cell division. Moreover, the protection of DNA integrity is essential to avoid transfer of damaged DNA into the next cell generation. This may be achieved by cell cycle arrest, allowing for induction of various DNA-repairing systems, or by infinite pausing of the cell cycle (senescence). Tumour cells may alter the signalling pathways of these normal functions to gain survival benefits, e.g., through avoiding cell death and promoting proliferation despite the presence of mutated DNA, through activation of oncogenes and up- or downregulation of cell cycle checkpoint-regulating proteins (61, 62).

Charged particle irradiation with protons is of increasing interest due to its different energy distribution in tissue, allowing for efficient doses to the tumour with less harm to normal tissue. The energy deposit from protons is denser than that of photons and causes a higher proportion of lethal DNA damage. It peeks deeper in the tissue within a narrow range, wherein almost all energy will be scattered and hit the tumour target. Contrastingly, photons have a continuously decreasing ionising effect along their path through the patient, thus harming tissues before, within and after the tumour target. The side effects and tumour effect of proton irradiation for RC is currently being explored within a Swedish randomised controlled trial comparing proton treatment with conventional photon treatment with identical delivered doses and fractionation (5 x 5 Gray (Gy)) (63). Protons and photons have slightly differing relative biological effectiveness and the clinical importance of this remains to be further studied (64).

Local irradiation, brachytherapy, is useful as treatment of RC in some situations. The radiation source is placed within or in contact with the tumour itself and irradiates it with particles or X-rays. This is an option when conventional surgery is not suitable due to comorbidity or other patient-related reasons, or in local residual or local recurrent disease. Most often, local therapy is used in combination with external irradiation, but can be administered alone. Contact therapy should only be used in small and exophytic tumours since the radiation only reaches a few millimetres into the tumour. (65, 66)

Radiation techniques

Modern treatment planning is based on contouring of the RT target and organs at risk on CT or MRI ‘slices’ which added together form accurate 3D images of the structures of interest. The delivery of radiation for RC was traditionally done with so-called box technique, i.e., with three or four fields and this technique is still useful in situations where modern techniques are not applicable or available. Modern RT is delivered with a rotational gantry allowing for treatment from multiple angles, either with intensity-modulated RT (IMRT) with multiple fields at fixed positions or as volumetric modulated arch therapy

(VMAT), delivering radiations beams continuously as the gantry rotates around the patient. Multi-leaf collimators shape the beams differently depending on the pre-defined doses in different parts of the target, and spare the surrounding tissues from high-dose radiation.

The use of CT and MRI in RT planning, combined with the modern radiation delivery techniques and image-guided adjustments of fields, results in high-precision treatment, adapted to the shapes and locations of the treatment target and organs at risk, at every treatment fraction. However, the rotational techniques have the disadvantage of giving a low dose of radiation to a greater proportion of normal tissue than the box technique, which has raised concerns about increased risk of secondary malignancies (67).

Fractionation and radiobiology

Total doses needed for appropriate tumour control probability (TCP) must be divided into smaller fractions to lower the normal tissue complication probability (NTCP). The relation between these two is the therapeutic window.

The rationale behind fractionation is based on differences in biological characteristics between normal and tumour tissue that affect their radiobiological responses and can be described by the four or five 'Rs' of RT (68): Normal cells have efficient DNA repair systems, while tumour cells are disorganised and less efficient in cell repair. Dividing the total dose into fractions spaced apart in time will therefore favour normal tissue (Repair). In general, cells are most vulnerable to DNA damage during cell division. Fractionation increases the probability of hitting tumour cells in this vulnerable phase of the cell cycle (Redistribution). The radiation damage triggers cell division, especially in early responding and rapidly proliferating normal tissue, and to some extent in tumours, allowing for renewal of the damaged tissue (Repopulation). Tumours are self-sufficient in blood supply; however, vascularisation is disorganised, which may result in hypoxic areas within tumours. Oxygen is essential to maximise the intended damage from irradiation through the action of free radicals. Optimised timing between fractions may increase access to oxygen in the hypoxic zones and thereby increase the probability of tumour cell death in each subsequent fraction (Reoxygenation). Radiosensitivity may be added as a fifth 'R', representing the inherent characteristics of tissues that affect their response to RT (60, 68).

Radiosensitivity and prediction of response

The response of a tumour or normal tissue to RT is dependent on the total dose, the fractionation schedule, including the overall treatment time, and the inherent characteristics of the tissue. The so-called Linear Quadratic model (LQ) is used in estimating the radiation effect on tissue. The model describes the cell survival fraction (SF) as a function of the radiation dose (D), accounting for the tissue's inherent radiosensitivity by including the two constants α and β (60). These constants represent different aspects of radiosensitivity and repair ability. α describes the single-hit DNA damages leading to DNA double strand breaks and cell death, and β reflects the cumulative sublethal damages, such as DNA single

strand breaks. The α/β ratio describes the sensitivity of tissue to RT and fractionation. A high α/β ratio, typical for certain tumours and early-responding tissues, means a high probability of irreparable cell damage and low repair capability. Such tissues will usually not gain much from the tissue-sparing effect of fractionation into many low doses. Late-responding tissues typically have a low α/β ratio and will be spared by fractionation, as they have low proportions of lethal damage and high capacity to repair sublethal damage.

Translation into equivalent doses of 2 Gy fractions (EQD2) is done to compare the expected biological effective dose (BED) of different fractionation schedules and to predict TCP and the NTCP (69), also accounting for the time between fractions. The higher the total BED, the smaller becomes the margin between the TCP and the NTCP, and the higher the risk of long-term side effects (70). Attempts to determine the α/β ratio for tumours have resulted in diverse estimates (69). Using different ratios when calculating the BED of a schedule may give very different estimates. In RC, α/β is suggested to be approximately 10 (71). However, the ratio has been debated, and one study proposed it to be close to 5 (72). The discrepancy in the suggested radiosensitivity may be due to the heterogeneity in RC tumour biology (60, 69).

Radiotherapy in rectal cancer

Preoperative or neoadjuvant (C)RT, as opposed to adjuvant (C)RT, is standard in Europe (35) based on randomised studies showing local recurrence rates favouring the neoadjuvant strategy (73-76). The indication for neoadjuvant treatment depends on tumour operability, tumour height and the risk of local recurrence. There is robust evidence for decreased local recurrence rates and improved survival by the addition of (C)RT to surgery, before implementation of TME surgery. In the Stockholm I trial, adding preoperative RT reduced the local recurrence by half compared to surgery alone (14% *vs* 28% $P<0.01$) (20). The Swedish RC trial confirmed the large gain in local recurrences and showed an improved OS (21, 77). These findings were supported by a meta-analysis (78) and systematic overviews (30, 74). The contribution of (C)RT to improved outcomes after the implementation of TME surgery was confirmed in the Dutch TME trial showing that the local recurrence rate at 2-year follow-up was significantly lower after preoperative RT and TME surgery than after TME surgery alone (2.4% *vs* 8.2%, $P<0.001$); the difference was still significant after 6 and 12 years (24, 79, 80). Trials after TME introduction have failed to show convincing gains in survival. However, in the TME trial, the 10-year cancer-specific survival was improved in stage III disease with negative resection margins in the RT group compared with surgery alone (50% *vs* 40%, $P=0.032$) (80).

Adding concomitant chemotherapy to long-course RT (CRT) results in a higher proportion of R0 resections and pathologic complete responses (pCR) and reduced local recurrences (81, 82). Randomised trials, systematic overviews and meta-analyses comparing pre- and postoperative treatment strategies show results in favour of preoperative treatment (30, 74-76, 78).

Local recurrence rates are low thanks to the treatment strategies listed above, and the main challenge lies in reducing distant recurrences and improving survival outcomes. A step forward has recently been taken through the implementation of sequential preoperative RT and neoadjuvant chemotherapy (83-86) (see below).

Radiotherapy target and schedules for rectal cancer

Radiotherapy is administered as either hypo fractionated short-course RT (SCRT) of 5 x 5 (Gy) or conventionally fractionated long-course RT of 25–28 x 1.8–2 Gy, with a boost of 3 fractions of 1.8 Gy to the gross tumour volume (GTV), including the rectal tumour and radiologically malignant lymph nodes. The standard schedule results in a total dose of 45 Gy to the clinical target volume with lymph nodes at risk of subclinical disease (CTVN) and 50.4 Gy to the GTVT. The Swedish (and international) standard for locally advanced tumours has been a long-course schedule concomitant with chemotherapy in radio-sensitising doses, primarily capecitabine (825 mg/m^2, twice daily) or if contraindicated, with (5-FU) bolus infusions. The practice has gradually changed to short-course RT with sequential full-dose chemotherapy.

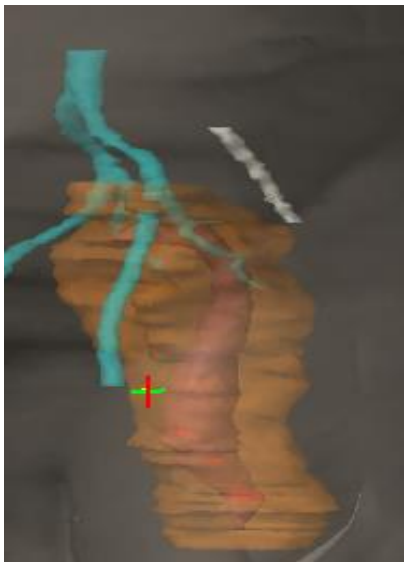

Figure 5. Delineated RT target for treatment planning. Orange: Clinical target volume including regional lymph nodes; Red: Gross tumour volume, rectum and mesorectum. Reprinted with permission from Dr C. Staff.

The RT target (*Fig. 5*) is defined based on international contouring and planning guidelines (65, 87, 88), to cover subclinical loco-regional disease in addition to the radiologically visible primary tumour, pathological lymph nodes and tumour budding. This results in a CTVN substantially more extensive than the rectal tumour per se. It covers the mesorectum and regional lymph node compartments, with the upper limit at the level of the bifurcation of the common iliac artery or the sacral promontory. The lower limit of the CTVT is 2 cm below the GTVT, and the CTVN encompasses the CTVT. Overgrowth to the sphincters or the *levator* muscle, invasion into the sphincter muscles and the locations of pathological lymph nodes are also considered, and the lateral and inferior borders are extended to cover these affected structures. In the dose planning target volume, a margin is added to the CTVN to account for movements of the target position and normal variations during the course of treatment (65).

Radiotherapy in rectal cancer in Sweden

In the algorithm used to determine the accurate treatment for every patient, tumours are categorised into three risk groups based on risk of local recurrence: low risk or ‘good’ (recommended surgery alone), intermediate or ‘bad’ (treated with RT + surgery), and high risk or ‘ugly’, requiring the addition of preoperative chemotherapy to RT to enable or facilitate radical and less extensive surgery). The allocation into a certain category depends

on the tumour's distance from the anal verge, the number and location of pathological lymph nodes, any signs of extra-mural vascular invasion (EMVI) and the local tumour growth in relation to the mesorectal fascia, the peritoneal fold, the sphincters and adjacent organs.

In Sweden, the proportion of RC patients receiving preoperative RT was approximately 60% in 2017 (*Fig. 6*), and the 5-year local recurrence rate was 3% in 2020 (2). Norway has recurrence rates similar to Sweden, although only 40% of patients receive preoperative RT (89). The proportion of Swedish patients treated with preoperative RT has therefore been suspected to be unnecessarily high (89).

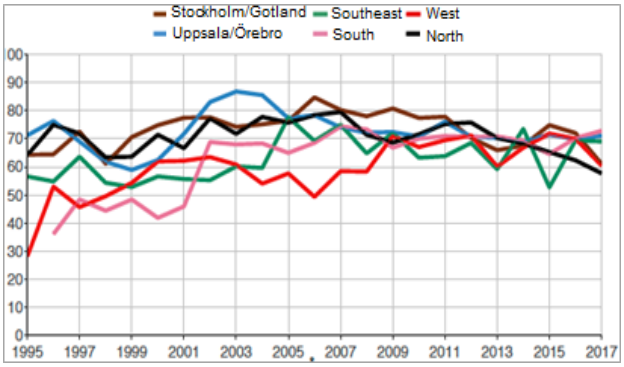

Figure 6. Proportion receiving preoperative RT among rectal cancer patients operated with AR, APR or HartmannRT) (1).

Consequently, the Swedish guidelines for RC were recently revised with the aim of decreasing the number of patients treated with RT to approximately 50% (65). The changes were based on a revision of the recurrence risk assessment. An increased number of tumours are now considered 'low risk', comprising high T3 and T4a (with limited peritoneal involvement), N1a, and N1b-c if primary tumour is in the upper part of the rectum. Tumours with these features were previously categorised as 'intermediate risk'. In addition, several features previously assessed as 'high risk' are now categorised as 'intermediate': T4a with more extensive peritoneal engagement, and selected T4b and N2.

Further, the previous standard treatment with long-course CRT, recommended in high risk tumours, has to a large extent been replaced by sequential short-course RT followed by combination chemotherapy as in the experimental arm of the randomised trial RAPIDO (SCRT + chemotherapy with capecitabine and oxaliplatin (CAPOX) x 6) (86). The LARCT-US trial regimen is discussed as an option with four instead of six cycles of CAPOX (90). Before the publication of the RAPIDO results, many Swedish oncology departments treated RC by the LARCT-US protocol, which is reflected in *Fig. 7*. As this change in the national guidelines depended primarily on the results of the RAPIDO, tumour characteristics that would have qualified for inclusion in the trial (T4b, N2 and EMVI) may be treated as 'high risk' tumours in accordance with the study protocol, although T4b and N2 may alternatively be treated as 'intermediate risk' features, as described above.

In the 3-year follow-up of the RAPIDO trial, the disease-related treatment failure (primary endpoint) was in favour of the experimental arm, as was the pCR (83). The decrease in disease-related treatment failure was primarily explained by fewer distant recurrences in the experimental arm, while no improvement was seen in local recurrence rates (83). The

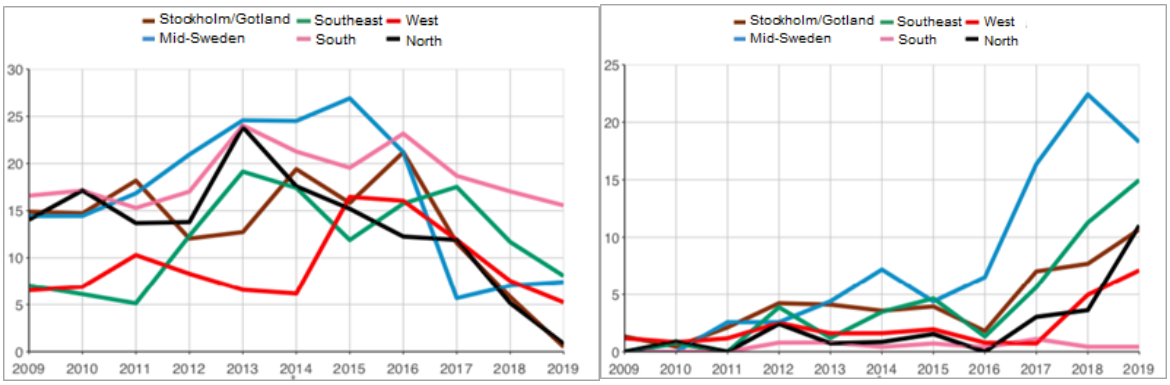

Figure 7.
Left: Proportion receiving standard CRT (90% with single 5-FU or capecitabin (not in figure))
Right: Proportion receiving short-course RT followed by chemotherapy (1).

benefit of neoadjuvant sequential treatment strategy was explored in a Polish study, differing from the RAPIDO treatment arms in that short-course RT was followed by only three cycles of FOLFOX and the control arm was a CRT regimen in which oxaliplatin was added to 5-FU (84). After three years, there was significant improvement in OS; however not in the 8-year follow-up (91), and there were no differences in local recurrences or pCR (84).

In line with the results of the RAPIDO, the Chinese STELLAR trial reported a two-fold increase in pCR for short-course preoperative RT followed by CAPOX x 4 *vs* standard CRT. Additionally, this study showed an improved 3-year OS and non-inferiority in 3-year disease-free survival (DFS) (92). The French randomised trial Prodige-23 allocated patients into standard treatment (CRT, surgery and adjuvant chemotherapy) with or without triple neoadjuvant chemotherapy (FOLFOXIRI) before CRT. The results were similar to those seen in the RAPIDO study: three-year DFS was significantly improved, primarily due to improved distant metastasis-free survival, there was no improvement in local recurrence rate, and the pCR rate improved significantly (85). Additionally, the neoadjuvant sequential treatment strategy resulted in fewer postoperative complications and less toxicity from chemotherapy (85).

Timing of treatment

The best timing for surgery following RT in the intermediate group has been debated (33, 93, 94), and practices changed in favour of delayed surgery (35, 65). In the Stockholm III trial, no significant differences in risk of local relapse, recurrence-free survival (RFS) or OS were seen following SCRT with immediate surgery, compared with delayed surgery. However, there was an increased rate of pCR when surgery was delayed (95). Both delayed surgery and very early surgery (within 2–4 days) lowered the risk of postoperative

complications (33). Further advantages of delayed surgery are the possibility to select patients with pCR for organ-preserving strategies, having time to optimise patients' general condition and thereby reducing the complications to surgery or, when indicated, to treat with neoadjuvant chemotherapy. On the negative side, acute side effects, primarily RT-induced enteritis and diarrhoea, have time to develop before surgery. Moreover, tumours resistant to RT remain without efficient treatment until surgery and adjuvant chemotherapy. Preoperative RT with immediate surgery has the advantage of short lead time to adjuvant chemotherapy; however, this becomes less important in light of the beneficial outcomes of incorporating chemotherapy in the neoadjuvant instead of adjuvant setting. Given that there are chemo-resistant tumours, available treatment predictive markers should be analysed before initiation of treatment, and early evaluation is needed to adapt the strategy when appropriate.

3.2.3 Adjuvant chemotherapy

The use of adjuvant chemotherapy in RC is based on evidence of improved DFS and OS in colon cancer. However, the corresponding improvements have not been proven in RC. A Cochrane review and meta-analysis from 2012 included RC studies from before and after the introduction of TME and the use of preoperative (C)RT (96). Improved DFS and OS

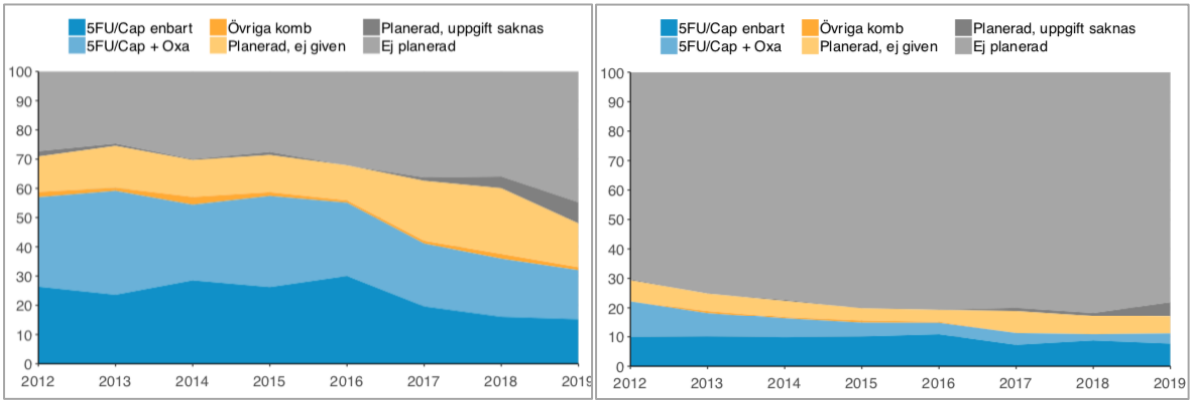

Figure 8. Adjuvant chemotherapy in patients operated for rectal cancer, age < 75 years (1). Left: pTNM stage III. Almost 35% received treatment. Right: pTNM stage II. Approximately 10% received treatment.

were present after adjuvant chemotherapy compared with observation (96). However, the use of adjuvant therapy was not supported by another systemic review and meta-analysis from 2014 which included four randomised trials, partly conducted in the setting of modern RT and surgical techniques (97). No improvements were observed in DFS, OS or distant recurrences when 5-FU-based adjuvant chemotherapy was compared with observation (97). Nevertheless, in the subgroup of high tumours (10–15 cm), there was a significant improvement of DFS and distant recurrences. Oxaliplatin improved DFS in the German CAO/ARO/AIO-04 study when added in both the neoadjuvant CRT and the adjuvant regimen (98), but the role of adjuvant combination therapy remains unclear (97). Despite weak evidence for a benefit, adjuvant chemotherapy after administration of preoperative

(C)RT differing degrees in different countries. The Swedish guidelines recommend adjuvant chemotherapy in stage II disease with risk factors for relapse and in stage III RC, if no preoperative RT is given, and opens for chemotherapy following short-course RT with direct surgery and with delayed surgery if the histopathology includes risk factors. According to the RC report from 2019, 10% and 35% of patients younger than 75 years had adjuvant chemotherapy in stage II and III, respectively (*Figure 8*).

The international IDEA study investigated the impact of the duration of adjuvant chemotherapy in stage III CRC. In the 5-year survival analysis from 2020, the criteria for non-inferiority set in the study for three months *vs* six months combination chemotherapy were not met (99). However, the absolute numerical differences in DFS and OS were considered clinically negligible. At the same time, the gain in lowered toxicity – most notably in peripheral neuropathy – was substantial, and the study supported three months to low-risk tumours. Due to an observed difference in outcome between the chemotherapy regimens the study also supports the use of CAPOX for three months in high-risk tumours; however, the evidence is based on a post hoc comparison between CAPOX and FOLFOX (99). Set in the context of less toxicity, three months of FOLFOX may also be preferred to six months, especially in low risk tumours, as proposed in the Swedish national guidelines (65). Only one of the IDEA trials involved patients with RC; however not powered for subgroup analysis of RC. Thus, the results above may not be valid for RC (100).

3.2.4 Organ-preserving strategy

Surgical resection has been the cornerstone of RC treatment with curative intention. During the last decades, it has become evident that a subgroup of RCs are highly sensitive to (C)RT and may respond with clinical complete response (cCR) to neoadjuvant oncological treatment. In the Stockholm III trial, 10.6% had cCR after SCRT and 4–8 weeks delay to surgery (33), and 23–28% in three of the above-mentioned trials investigating neoadjuvant (C)RT and sequential chemotherapy (83, 85, 92). In these cases, an organ-preservation strategy with close and extended follow-up, without surgical tumour resection, may be an alternative to surgery. If tumour regrowth occurs during follow-up, salvage surgery can be performed. A Brazilian research group first explored such organ-preserving strategies in early tumours (101). Several studies worldwide are investigating similar organ-preserving concepts, referred to as the Watch-and-Wait or Watchful Waiting (W&W) strategy. In the international, multicentre STAR-TREC trial, patients with radiological T1–3b or N0 tumours are randomised to either standard TME surgery (control) or to a potentially organ-saving strategy, using CRT or SCRT Gy followed by active surveillance in case of complete clinical response (102). The Swedish W&W programme includes patients who had cCR from preoperative treatment following the recommendations in the national guidelines, i.e., for locally advanced or very low tumours (103). An analysis from 2021 reported regrowth in 17 of 88 (19%) patients after a median follow-up time of 2.8 years, and 16 of 17 had salvage surgery (104). The organ preservation rate was 81%, and the

estimated 3-year survival rate was 93% in all patients (104). The results are in line with those of a previously published large international multicentre study based on data derived from the International Watch and Wait Database (IWWD) (105): In the 880 included patients with cCR, the regrowth rate was 25% of which 88% occurred during the first two years. The 5-year cancer-specific survival and OS among patients with regrowth were 84% and 75%, respectively and 97% and 88% in patients without regrowth (105). Unresectable recurrences were rare in both studies.

3.3 ADVERSE EFFECTS OF RECTAL CANCER TREATMENT

Acute side effects of preoperative RT occur within a few weeks of treatment and include diarrhoea, enteritis, cystitis, sacral pain and hematologic toxicity due to bone marrow suppression. If chemotherapy is part of the treatment, fatigue becomes more common, the risk of diarrhoea and hematologic toxicity increases, and peripheral neuropathy can occur if treatment includes oxaliplatin. In the long term, preoperative treatment and surgery may result in impaired functional outcomes characterised by loss of the rectum storage function and dysfunctions of pelvic organs and structures in the proximity of the rectum. The surgical trauma, with potential damage to autonomic nerves and blood supply (106-108), and inflammation and progressive fibrosis from RT contribute to the negative effect on adjacent organs (109). Bowel, urinary and sexual problems, altered gonadal function, and impaired bone health with risk of pelvic insufficiency fractures are common and may result in chronic morbidity with a negative impact on quality of life (QoL) among cancer survivors (110-123). Background information for the side effects most relevant to this thesis is provided below.

3.3.1 Bowel function

Most patients with low AR suffer from either incontinence for flatus, liquid stools or both, increased frequency and clustering of bowel movements, or increased urgency. These symptoms, referred to as Low Anterior Resection Syndrome (LARS), may have a severe negative impact on QoL and seem persistent, at least for many years treatment (124-126). Various patient- and tumour or treatment-related factors impact the severity of LARS: age, sex, sphincter and bowel function before surgery, tumour distance from the anal verge, total *vs* partial mesorectal excision, the use of preoperative RT, and presence of temporary stoma (127). A temporary stoma routinely accompanies low AR of the rectum with anastomosis. It reduces short-term overall mortality and anastomotic leaks and does not affect the long-term oncological outcome. (128, 129). In the first randomised trial comparing outcomes between participants who had a stoma or not, leakage occurred in 10% and 28%, respectively (45). Reversal of the loop-ileostomy is usually recommended about three

months after resection of the primary tumour. However, it is often delayed due to, e.g. ongoing chemotherapy, lack of surgical resources or leakage from the anastomosis (130). Although the loop-ileostomy is intended to be temporary, it is reported to increase the risk of having a permanent stoma compared with direct anastomosis (45, 129). Other complications from the diverting stoma are dehydration and the risk of renal failure (131). Early (7–13 days postoperatively) loop-ileostomy closure is a concept reported to be both safe and cost-effective in selected patients with a low risk of anastomotic leakage (132-134). In patients with multiple risk factors for a poor functional outcome, a permanent colostomy should be considered, particularly in frail patients for whom a complication such as anastomotic leakage could lead to severe morbidity or even mortality. However, a permanent colostomy is also associated with a negative impact on QoL (118, 135, 136).

Before the development of the LARS scoring system, there was a lack of consensus on how to assess bowel incontinence. In 1988, Miller et al. developed a three-grade scoring system based on frequency and type of incontinence (flatus, liquid stools and solid stools) (137). The classification of frequency grades I–III was later modified to enable distinguishing between patients with more frequent incontinence than in the original scoring system (138).

3.3.2 Bone health

Insufficiency fractures

Insufficiency fractures in the radiation field are a troublesome late complication with a high burden of morbidity and risk of increased mortality (139). An insufficiency fracture may be provoked by normal physiological stress or traumatic stress on abnormal bone, and is typically present in or close to the pelvic bones (140, 141). Several studies have identified an increased incidence of pelvic insufficiency fractures (PIFs) after radiation therapy for pelvic malignancies other than RC (142-144). In cervical cancer survivors, a recent literature review and meta-analysis reported the incidence to vary from 1.7% to 89% in previous publications; the pooled prevalence of PIFs in the meta-analysis was 14% (95% CI 10%–19%) (143). Another meta-analysis of cervical cancer studies reported almost identical incidence (14%, 95% CI 10%–18%), a median time to fracture of 7.1–19 months and the most common site as being the sacral joint or the sacral body (142). Similarly, in a review and meta-analysis from 2020, the 5-year incidence among gynaecological cancer patients was 15% (95% CI 8%–25%) (144).

The reported incidence following RC treatment differs markedly between studies. (Chemo)RT for RC, compared with surgery alone, increased the risk of PIFs after 2–4 years with a HR of 1.7 (95% CI 1.2–2.5, P=0.008) in a large propensity-matched study where 21% of the irradiated patients were diagnosed with PIFs, with a median time to fracture of 2.5 years (145). In a prospective Danish study, 34% (95% CI 25%–42%) of patients treated with CRT were diagnosed with PIFs after 3 years, compared with 3.5% (95% CI, 9%–15%) after surgery alone (123). A retrospective study of 492 RC patients who received (neo)adjuvant CRT reported an incidence of 7.1%, primarily located in sacral bone, and

with a median time to fracture of 3.8 years (146). Identified risk factors of insufficiency fractures are female sex, menopause, age above 60 or 65 years, osteoporosis, low body mass index (BMI), long-term medication with corticosteroids or bisphosphonates, rheumatic disorders and muscle atrophy or sarcopenia (123, 145, 146).

Bone has high density and absorbs high radiation doses, making it a common site for radiation-induced damage (147). Histopathological changes in bone after RT include hypo-vascularity, hypocellularity and fibrosis (148). The damage observed within the bone after irradiation is similar to the pathological conditions of osteoporotic bone, including a decrease in trabecular bone volume (149). One major cause of impaired bone health after RT appears to be the decreased blood supply caused by fibrosis of vessels in combination with damaged vessels from surgery and may lead to osteonecrosis (150). To predict which factors are associated with the development of PIFs, research focusing on baseline assessment of bone health has been suggested (139). The radiation dose to the pelvic bone and specifically to the sacrum where most PIFs occur, is influential in the development of PIFs (151, 152).

Bone remodelling

There is a continuous resorption of old or damaged bone and formation of new bone, *bone remodelling*, which serves to maintain bone mass and strength and to ensure calcium homeostasis. Osteoclasts are bone resorbing cells which form trabecular and cortical bone resorption cavities. The osteoblasts are responsible for bone formation, and are recruited to the cavities, which they fill with osteoid that is subsequently mineralised. The resorption phase is shorter (weeks) than the formation phase (months). In healthy bone, the resorption

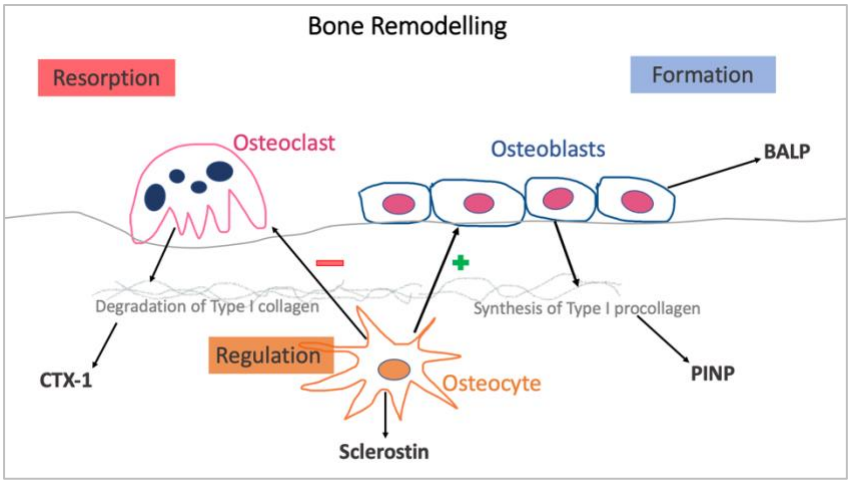

Figure 9. Schematic illustration of bone remodelling. Bone biomarkers used in Study IV: Carboxy-terminal crosslinking telopeptide of type I collagen (CTX-I), Amino-terminal propeptide of type I procollagen (PINP); Bone specific alkaline phosphatase (BALP).

and formation processes are sequentially 'coupled' and in balance. When they are not, bone morbidities will develop (153).

A number of peptides are released from type I collagen and procollagen during the resorption and formation phases, respectively (*Fig. 9*). Together with proteins secreted by

the bone-remodelling cells, these molecules are referred to as bone turnover markers (BTMs), reflecting the activity and numbers of bone cells involved in the remodelling process (153). They are measurable in ordinary blood samples, creating a practical way to assess bone remodelling. Bone-specific alkaline phosphatase (BALP) is secreted by activated osteoblast and is a frequently used bone formation marker (*Fig. 9*)

A third cell type - the osteocyte - has an essential regulatory role in bone remodelling, mediating its effects primarily through the release of sclerostin (*Fig.9*). Osteocytes are important for the positive effects on the bone from mechanical stimulation. Bone metabolism is strongly dependent on the Wnt signalling pathway which, when activated, leads to increased bone mass, while inactivation leads to bone loss. Sclerostin is a crucial regulator of bone formation through its inhibitory effect on Wnt signalling, leading to inhibition of osteoblastogenesis and bone formation (154). Beyond this primary way of action, sclerostin also stimulates osteoclastogenesis and bone resorption, reinforcing the loss of bone mass (155, 156).

Interest in implementing the use of BTMs in the clinic is increasing. To date, the recommendation for clinical use of bone markers is limited. In 2019, a European consensus group reported that the BTMs carboxy-terminal cross-linking telopeptide of type I collagen (CTX-I) and amino-terminal propeptide of type I procollagen (PINP) are preferred for use as estimates of bone turnover in the clinical setting because they are specific for bone, robust in clinical studies and widely used (157). However, there are various factors affecting BTM levels, some of which are controllable (e.g., food intake, exercise and lifestyle factors) and others not (e.g., age, sex, menopausal status and comorbidity) (158). A meta-analysis from 2019 evaluated the predictive value of CTX-I and PINP for future fractures and found that they modestly improved fracture risk prediction when added to bone mineral density (BMD) and established clinical risk factor assessment tools (159). Accordingly, CTX-I and PINP could be seen as a complement to the established tools in fracture prediction, although they are not recommended to be used alone for this purpose. In line with these results, the consensus group stated that BTMs have limited predictive value for fractures (157). The authors further concluded that the clinical use of BTMs lies primarily in assessment of compliance to oral bisphosphonates in osteoporosis. However, BTMs are not useful in evaluation of the treatment effects of bisphosphonates.

A Cochrane analysis from 2018 reviewed studies of preventive measures of radiation-induced pelvic bone damage and concluded that there was an important lack of evidence in this field (150). The authors identified a need of future interventional trials, including of patients planned for pelvic irradiation, where BTMs could be used as surrogate markers of bone health through prospective and repeated measurements during treatment follow-up, in addition to BMD and radiology results.

Factors with impact on bone turnover and BTMs

One of the factors with greatest impact on bone turnover is sex, especially after menopause. During the menopausal transition, bone turnover increases markedly and remains high and stable (153, 158). Among the diseases expected to increase bone turnover are hyperparathyroidism, thyrotoxicosis, hypogonadism, vitamin D-deficiency, severe chronic kidney disease and fractures. Rheumatoid arthritis and osteoporosis lead to uncoupling of bone turnover, with increased resorption. Medication for osteoporosis strongly impacts bone turnover, with PINP and CTX-I expected to decrease drastically from bisphosphonates (resorption inhibitors) and to increase from stimulators of bone formation. Vitamin D and calcium supplements lead to a moderate and dose-dependent decrease in BTMs (158). Oral and parenteral glucocorticoids induce bone loss and lead to increased fracture risk (160). The effect depends on dose, duration of treatment, and the underlying disease. A decrease in PINP can be expected from glucocorticoids, while the effect on CTX-I is not clear (158). Moreover, BTM levels may show circadian variation and change with food intake, exercise, smoking and alcohol consumption (153).

Radiotherapy and bone cells

Most data on the cellular damage in bones from RT derive from *in vitro* or animal studies (161). The osteoclasts increase in number and activation in the acute phase, probably due to a direct effect on precursor cells and indirectly via proinflammatory cytokines known to stimulate resorption, together leading to increased bone resorption. In contrast, the osteoblasts decrease both in number and activity due to apoptosis, DNA double strand breaks and cell cycle arrest in murine models, resulting in decreased bone formation. Bisphosphonates are anti-resorptive and had protective effects against bone loss in mice, although without effect on the biomechanical quality on the bone (162, 163), and anti-sclerostin antibodies was protective of bone formation after irradiation in animal studies (164). The anabolic osteoporosis treatment teriparatide had a protective effect on osteoblasts and an activating effect on the Wnt/catenin pathway by inhibition of sclerostin, and thereby prevented DNA damage in osteoblasts and apoptosis (165, 166). Osteocytes appear to be the most radiosensitive of the three bone cell types (161). Low-dose RT leads to osteocyte death *in vitro*, but increased sclerostin secretion in murine models.

3.3.3 Sex hormones and fertility in females

The RT target for RC comprises the ovaries due to their proximity to the rectum. The ovaries constitute a principal source of endogenous female sex hormones in premenopausal females and are an important source of androgens in females of all ages (167).

In premenopausal females, the ovarian production of oestrogen and progesterone is regulated by the hypothalamus-pituitary gland-gonadal axis. The gonadal hormones exert

negative feedback on the gonadotropic-releasing hormone secreted by the hypothalamus, which in turn stimulates the pituitary gland to release follicular-stimulating hormone (FSH) and luteinising hormone (LH), regulating the follicular maturation and the menstrual cycle. This will alter the local synthesis and levels of oestrogens and progesterone secreted into the blood, reaching the wide range of tissues with receptors for these hormones. The follicles are gradually depleted, at different speed depending on age, until all follicles have undergone apoptosis or entered senescence, and a complete loss of function occur with menopause as a consequence. Menopause is defined as the permanent cessation of ovulation and consecutive amenorrhea during 12 months (168, 169), and its natural onset is largely genetically determined (169). Following menopause, the oestrogens derive from peripheral conversion of pro-androgens in various locations; e.g. the adipose tissue, skin, bone, genitals, breasts, and CNS. In menopause, oestrogen primarily mediates its effect locally, through intracrine or paracrine mechanisms, and will barely have any systemic effects because of the very low serum levels (170, 171).

In females, androgens originate from the ovaries and the adrenals in approximately equal amounts, as well as from peripheral conversion (172-174). The proportions synthesised at different sites vary among the androgens and between pre- and postmenopausal females (174). Serum testosterone (T) originates from the ovaries and the adrenals in approximately equal amounts, from direct synthesis in the ovarian stroma cells and by peripheral conversion of A-4 mainly produced in the adrenals (167). The proportion of T produced in the ovaries increases after menopause, whereas the proportion of androstenedione (A-4) decreases. However, the serum levels of androgens do not change specifically during the menopausal transition. Instead, the androgens decline gradually with age at varying speed (172, 174, 175). Testosterone declines most in the early reproductive years, and Dehydroepiandrosterone sulfate (DHEAS) – the most abundant pro-androgen - declines most with age of all androgens (167), and originates from the adrenals both pre and post menopause. Surgical oophorectomy reduces T levels by approximately 30–50% (172, 174, 176).

The ovarian follicles are sensitive to oncological treatment (177-182). Half of the oocytes die from a dose < 2 Gy to the ovaries and a high risk of persisting amenorrhea is reported from total doses of 6 Gy (179, 183). The doses given for RC are therefore expected to cause iatrogenic menopause in most premenopausal females (184). Female fertility is dependent on the follicle pool, also referred to as the functional ovarian reserve (185). The ovarian reserve can be assessed by measuring serum levels of anti-Müllerian hormone (AMH), produced by the early ovarian follicles (185, 186). AMH is essential in the regulation of follicular maturation and oestrogen production, and selection of dominant follicles (186). The closer a female is to menopause, the higher the risk of iatrogenic infertility from cytotoxic treatment (187).

The effect of RT on ovarian androgen production is not fully known. A potential RT-induced androgen deficiency could be a treatable contributing factor to the sexual dysfunction, commonly reported following RC treatment. As regards gynaecological cancers treated with RT, information on ovarian testosterone production is limited and conflicting (188-191). Data indicate that the ovarian stroma, where the ovarian-derived androgens are produced, is less radiosensitive than the follicular tissue where oestrogen is synthesised (188, 189, 192, 193). Among the different categories of chemotherapy, the alkylating agents in general have a gonadotoxic effect. The platinum compound oxaliplatin used in CRC appear to have a minor and transient effect on the ovaries, although data are scarce, and figures and outcome variables vary in two retrospective studies evaluating amenorrhea and sex hormones in CRC patients (178, 194). In a recent prospective study, no permanent changes in oestrogen, LH, and FSH were observed following adjuvant chemotherapy in CRC (195).

Serum levels of sex hormones have an impact on sexual function in females and males. There are conflicting results on whether endogenous androgen serum levels correlate with sexual function in females (196-201). Observational studies have reported an association between endogenous T levels and sexual desire and sexual arousal response (197, 202, 203), and sexual activity (202). However, the most robust evidence for the impact of T on sexual function in females comes from clinical trials exploring the effect of T after oophorectomy and natural menopause. In this group of patients, T substitution had a positive influence on desire according to several studies (203-207). Androgens receptors are present in various tissues, e.g. in the vagina. Testosterone is suggested to modulate vaginal physiology by promoting the relaxation of smooth muscles, leading to increased blood flow, and thereby contributing to female sexual arousal and lubrication (208).

3.3.4 Sexual function in females

Sexual life is an important aspect of an individual's QoL and is influenced by physiological, contextual, psychosocial factors, e.g., partner relationship, partner sexual function and psychological well-being (3). Morbidities such as diabetes, cardiovascular disease and cancer have a potentially negative impact (209). Sexuality in humans was historically described in a linear way, starting with sexual desire and ending with orgasm and resolution. This description did not capture the complex nature of either female or male sexuality. The clinical psychiatrist Basson developed a circular model of the female sexual

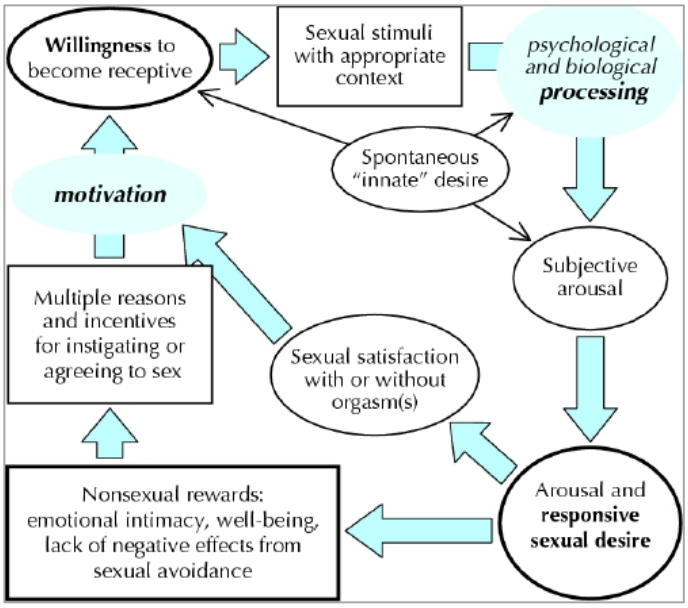

Figure 10.
The Female sexual response cycle, as described by Basson R. Women's sexual dysfunction: revised and expanded definitions (3) Reprinted with permission from the Canadian American Association Journal.

response (210). This conceptualisation of the sexual response has been widely adopted and referred to in the literature, and the model has been developed further (199). The model suggests that a normal female sexual response does not necessarily start with a spontaneous sexual drive, but may begin from neutrality. The sexual desire may arise after sexual arousal, which in turn occurs due to either biological or psychological, internal or external, stimuli. Once arousal and desire are present and lead to emotional and physical satisfaction, a positive experience will increase a behaviour of seeking or being responsive to sexual stimuli in the future (*Fig. 10*). The different phases of the cycle may overlap and do not always follow the same order (211).

Female sexual dysfunction (FSD) has been classified differently over time. Among the sexual disorders described in the standard classification of mental disorders from 2013 (DSM-5), sexual interest and arousal disorder and orgasmic disorder are common in females (212). Following RC treatment, impaired sexual function is common in both males and females (107, 108, 119). This is less studied in females than in males (119), and the response rates to questionnaires investigating the topic tend to be lower in females than in males (119, 213). The decrease in sexual function may depend on anatomical, physiological and psychological adverse effects from the cancer disease per se and its treatment. Few

studies have specifically studied sexual function in females after RT for RC as a primary outcome, but there are several studies on the effect from pelvic irradiation for gynaecologic malignancies (214, 215).

Surgery for RC may cause scarring, nerve damage and anatomical changes affecting sexual function in both males and females (107). There is a risk of injury to the pelvic hypogastric nerve plexus and its branches at different levels, affecting nerves that regulate parts of the female sexual response cycle, i.e. lubrication and orgasm (106). The damage to nerves may be further aggravated by radiotherapy. Previous studies reported vaginal dryness and dyspareunia in 60% of females and severe impairment of erectile function and retrograde ejaculation in 80% of males after RC treatment (108, 120, 121, 216). Scarring and permanent or temporary stoma can reduce self-esteem and contribute to a negative body image (116, 121, 136). Following an abdominoperineal resection of the rectum, a dorsal-caudal dislocation of the uterus and vagina may results in a vagina with a horizontal position, parallel to the pelvic floor, and an angulation of the introitus (217). This, in turn, leads to mechanical obstruction with an accumulation of secretions and risk of secondary infections, and affected sexual function. Vaginal resections may obviously affect sexual function although reconstructions are made.

Pelvic RT has been pointed out as a risk factor of FSD following RC treatment (112, 114, 116, 136). Three of these studies were cross-sectional and one prospective, and the questionnaires used were the Sexual Function Vaginal Changes Questionnaire (SVQ), the Rectal Cancer Female Sexuality Score (RCSF) and one non-validated questionnaire. Radiation-induced synechiae and vaginal narrowing can aggravate vaginal dysfunction and make intercourse impossible or painful. An inability to have sexual intercourse due to pain, discomfort or wound healing problems is common after extended APE with resection of the posterior vaginal wall and a muscular flap reconstruction, according to limited data (218, 219). Radiation-induced pelvic inflammation with consecutive fibrosis, combined with the surgical injury of autonomic nerves, are possible pathophysiological mechanisms resulting in sexual or urinary dysfunctions (106, 114, 214, 215). Moreover, low AR syndrome with faecal incontinence may negatively impact sexual function (117). A review of sexual outcomes in females after pelvic RT for pelvic malignancies highlighted vaginal problems as a major cause of sexual dysfunction (215). Following RT for cervical cancer, survivors have reported a lack of sexual desire, arousal, lubrication and satisfaction and dyspareunia (220).

The impact of different approaches to rectal resection on female sexual function has been explored in several studies. No clear benefit was found for either method when comparing open and laparoscopic surgery (221-223). A recent review and meta-analysis comparing laparoscopic and robotic surgery for RC could not draw any conclusions regarding superiority in terms of female sexual function (221).

Chemotherapy and sexual function

According to studies among breast cancer patients, chemotherapy may affect sexual function in several ways (180, 183, 194, 224, 225). Vaginal dryness and pain during intercourse or caressing can be related to physiological changes secondary to ovarian failure caused by alkylating agents and high-dose regimens. The agents used in curative treatment of RC are 5-FU, its peroral prodrug, capecitabine, and oxaliplatin. The former two may cause dry and sensitive mucosae, being a possible reason for sexual dysfunction. Oxaliplatin may cause a transient ovarian failure, and there is no data on whether the peripheral neuropathy could affect sexuality. The chemotherapy in the standard CRT regimen is administered in low doses with the primary aim to enhance the effect of RT, and the systemic effects, such as nausea, diarrhoea and fatigue are normally mild. These could, however, negatively influence sexual function. Nevertheless, these agents are not described as causing sexual dysfunction in the literature (181).

Addressing sexual function with patients

As described, rectal cancer treatment involves several side effects that can be sensitive to discuss: changed anatomy including stoma, (partial) resection of adjacent organs or tissues resulting in altered physical appearance, impairment in bowel and urinary function with risk of incontinence, and affected sexual health including fertility (112, 114, 119, 216). Sexuality is a private matter, so asking patients to share information about this may be perceived as intrusive, depending on a patient's culture, age, personality and how questions are asked. However, clinical experience and data from earlier studies indicate that patients in general do not find discussions and information about sexual matters problematic, and that there are unmet informational needs (226, 227). Among patients with sexual dysfunction affecting daily life following rectal cancer treatment, 20–25% reported in an online survey that they would have changed their treatment decision had they known of these side effects beforehand (228). According to a frequently cited study from 2005, only 1 of 10 females treated for RC remembered having discussed sexual matters with the doctor preoperatively, but with growing awareness of the problems (108), this figure may have improved. Still, in a retrospective Swedish study from 2020, only 169 of 378 (16%) and 67 of 326 (21%) of females remembered having discussed sexual function before treatment or at 1-year follow-up, respectively (229).

Research exploring the informational habits among Dutch surgeons and oncologists report that physicians sometimes avoid addressing sexual side effects with patients due to fear of causing patient discomfort or because patients do not raise the topic (230-232). Other commonly described obstacles to information among physicians were the patient being old or too ill. Both age and chronic illness are known risk factors for impaired sexual function. Among Swedish 70-year-olds, however, the proportion sexually active (defined as having intercourse) increased from 47% to 66% in males and from 12% to 36% in females in 1971–2001 (233), and sexuality may be important to QoL despite chronic illness affecting sexual function (199, 234).

3.3.5 Assessment of female sexual function

Female sexual function index

In the present cohort study, sexual function was measured with the Female Sexual Function Index (FSFI). The questionnaire was developed primarily as a way of measuring arousal in females which, unlike arousal in males, is difficult to measure in a laboratory setting. The instrument was developed to meet the need for a tool that took into account the multidimensional nature of FSD and discriminated well between females with female sexual arousal disorder and controls (235).

The FSFI is a 19-item, multiple-choice, self-assessment tool, validated for use in the general population (235-237), and reported to have good internal consistency, reliability, and criterion validity (238). It is recommended for use among cancer survivors and cancer patients by the Patient-Reported Outcome Measurement Information System and the National Comprehensive Cancer Network (239-241). The FSFI covers six domains of sexual function in females: desire, arousal, lubrication, orgasm, satisfaction and pain. A total FSFI score can be calculated when all items are completed and ranges from 2 (low function) to 36 (high function). The total score is the sum of weighted domain scores. Fifteen items have the response option 'no sexual activity' or 'did not attempt intercourse', which can be interpreted as no sexual activity occurring due to lack of option or as sexual function being impaired to the degree that sexual activity was not possible (240). The questionnaire is validated in females with hypoactive sexual desire disorder (235) orgasmic and hypoactive desire disorders (237), and multiple sexual dysfunctions (236).

Using the FSFI in individuals with low or no sexual activity is problematic; however, the definition of being 'sexually active' varies. Baser et al. suggested that females answering 'zero' ('no sexual activity' or 'no attempt to intercourse') or had missing answers for ≥8 of 15 items with 'zero' options, were not sufficiently active for the FSFI to be valid (240). They recommended against using the FSFI in case of sexual inactivity, as did Meston et al., who argued against calculating the FSFI score if any zeros are present since this may inflate differences between compared treatment groups, and the results will not represent participants' accurate sexual function levels (242). In the original scoring instructions, Rosen et al. suggested that 'zero' be treated as the lowest possible score for each item. In contrast, Meyer-Bahlburg explained the 'zero' options as conceptually different from other response options (243). Further, the questionnaire has been criticised by sexual and gender minorities for being hetero- and cis-normative in line with many other evaluation tools (244). There is no established minimal clinically important difference, but there is an established cut-off score of 26.55 for sexual dysfunction. The cut-off was defined in 2005 in the context of only sexually active, young females (mean age 36 years (range 18–74)) with different types of sexual dysfunction disorders as well as healthy controls (236).

Other assessment tools

The European Organisation for Research and Treatment of Cancer's (EORTC) QoL questionnaire QLQ-CR38 was developed for evaluation of QoL in CRC, and contains one item on sexual interest, sexual activity and sexual enjoyment, valid for both males and females, and two female-specific items on vaginal dryness and dyspareunia, respectively (245). It was further revised in the QLQ-CR29, with two female-specific items on sexual interest and dyspareunia, respectively (246, 247). The EORTC questionnaires are widely used (121, 122, 216), but have limitations. The QLQ-CR29 covers few aspects of female sexual function and its use is restricted to participants who have had intercourse during the preceding four weeks (247). The SVQ was constructed in 2004 by a Danish research group for use in gynaecological cancer patients (248). It is comprehensive concerning vaginal changes and other important domains of sexual function, and has been used in studies of RC patients (112, 114, 117). With the aim of obtaining a tool for use in RC, short enough to be suitable for screening in the clinical setting, a Danish research group recently created the RCSF (249). The questionnaire was developed from the SVQ, and has the advantage of discriminating for dysfunction that has negative impact on QoL (249). Despite its brevity, it captures psychological and disease-specific physiological aspects of the female sexual response sexual cycle. It is validated exclusively in sexually active RC survivors (249).

4 RESEARCH AIMS

The overall aim of the thesis was to increase knowledge about long-term adverse effects from RC treatment including preoperative RT in females with non-metastatic disease, stage I–III.

Specific aims

Study I

- Primary: To explore if preoperative RT for RC was associated with androgen levels in females.
- Secondary: To assess associations between androgens and sexual desire in females with RC.

Study II

- Primary: To investigate if preoperative RT for RC was associated with change in sexual function.
- Secondary: To assess the ovarian reserve after RC treatment in premenopausal females.

Study III

- Primary: To assess associations between serum levels of endogenous androgens and overall sexual function in females with RC.
- Secondary: To assess associations between androgen levels and different domains of sexual function.

Study IV

- Primary: To investigate if preoperative RT for RC was associated with changes in bone biomarkers in females.
- Secondary: To assess the incidence of radiation-induced pelvic bone damage and associations between changes in serum bone biomarkers and bone damage in females with RC.

Study V

- Primary: To investigate the extent to which RC patients got information about adverse sexual side effects, according to physicians and patients.
- Secondary: To explore if patients experienced unmet informational needs and identify barriers to information about sexual side effects.

5 MATERIALS AND METHODS

5.1 OVERVIEW OF THESIS

Table 2
Overview of thesis

	Main Cohort	Study I	Study II	Study III	Study IV	Study V
Inclusion period	June 2008 Dec 2013					Cohort 1: March-Apr 2022 Cohort 2: Apr 2017-July 2020
Study design	Prospective, longitudinal cohort study					Cross-sectional cohort study
Follow-up	Dec 2015	1 y postop	2 y postop	1 y postop	5 y postop	-
Inclusion criteria	Women diagnosed with RC stage I–III planned for abdominal surgery Age ≥18					Cohort 1: Physicians active in RC last 3y Cohort 2: Patients: Sthlm-Gtld, RC, abdominal surgery
Exclusion criteria	Inability to leave informed consent due to linguistic or cognitive restrictions Life expectancy < 2 years					Cohort 2: Surgery at Karolinska University Hospital or Ersta Hospital Missing in all items of interest
Additional exclusion criteria	-	History of oophor-ectomy	No FSFI completed	No FSFI, Sexual inactivity	No serum samples available	-
N, included **Total** Karolinska Ersta Örebro Norrköping Linköping	 142 64 50 12 9 6	125	139	99	134	Cohort 1: 186 Cohort 2: 253
Exposures / Predictors	RT	RT	RT	Androgens	RT	Participant's and clinical characteristics
Outcome measures	FSFI PGWBI, Sex hormones, Bone biomarkers	Change in androgens, Assoc. androgens sexual desire	Change in FSFI, Ovarian reserve	Assoc. androgens -FSFI	Change in bone biomarkers Prevalence bone injury Assoc. biomarkers bone injury	The extent of information on sexual side effects provided (Cohort 1) and perceived (Cohort 2)

RC, rectal cancer; RT, radiotherapy; FSFI, Female Sexual Function Index; PGWBI, Psycholgical General Well-being Index, Assoc., association; y, years.

5.2 STUDIES I–IV

Studies I–IV were based on the cohort study *Female Sexual function and well-being in women with rectal cancer*. The setting, participants and different variables are described below.

5.2.1 Participants

The Female Sexual Function and Well-being Study

The participants in study I–IV derive from the study *Female Sexual function and well-being in women with rectal cancer*. The cohort study was planned with the aim of describing sexual function, psychological well-being, sex hormones, markers of bone and muscle metabolism, and the frequency of benign oophorectomy, and to explore how rectal RC treatment affected these variables in females with RC stage I–III. The study was registered at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT01216189).

Screening and inclusion

Women with newly diagnosed RC were screened for study inclusion at preoperative MDCs at five Swedish referral centres for CRC: Karolinska university hospital, Ersta hospital, Örebro university hospital, Norrköping hospital, and Linköping university hospital.

Study I examines the impact of RT on ovarian function. Therefore, it excludes women with a history of oophorectomy or women who underwent oophorectomy concomitantly with resection of the primary tumour. Additionally, women who underwent oophorectomy during RC surgery were included in the analyses before but not after the procedure.
Study II examines the impact of RT on sexual function. Therefore, it excludes women who did not complete any of the FSFI items at any time point.
Study III examines the impact of androgens on sexual function. In the first draft of the manuscript, women who were and were not sexually active were analysed and reported separately. The final (published) version reports only on sexually active women.
Study IV examines the impact of RT on markers of bone metabolism. Inclusion was restricted to the participants for whom serum samples were available for laboratory analyses.

Power

Sexual function (Study II and III): According to the initial power calculation, 30 participants would be sufficient to detect a clinically relevant decrease in FSFI score. This was based on previously published FSFI-data from a validation study (237) in which the clinically relevant decrease of FSFI-scores was considered to be the difference in scores between the control group and the group with sexual dysfunction. Baseline sexual function cannot be assumed normal in the current cohort because of the high median age in rectal cancer. For that reason, 60 instead of the calculated 30 participants were estimated to be

sufficient to detect a clinically significant decrease in FSFI over time. A re-calculation of power was performed after a pre-planned interim-analysis in 2012, and was based on the mean FSFI total score at baseline of the included patients (250). The number needed was 99, and after correction for non-parametric statistics, 115. Compensating for expected loss to follow-up, the number needed to detect a hypothesised decrease in FSFI score with 3.0 (20% of the mean score of 15.0) was 140 (251).

An additional power analysis based on testosterone was performed and compensated for non-normal distribution and an age-dependent decrease in serum testosterone. Assuming a mean testosterone value at baseline of 0.66 nmol/l (172) and a reduction in the exposed RT+ group equal to that of bilateral oophorectomy (40%), a sample size of 16 participants in each group resulted in a power (1-beta) of 0.80 with two-sided confidence intervals of 0.95 (1-alpha).

5.2.2 Data sources

Swedish Colorectal Cancer Registry, and medical records and visits

Clinical data on the multi-disciplinary team assessment, ASA-classification, tumour and patients characteristics, and planned and obtained treatment, were retrieved from the Swedish Rectal Cancer Registry and medical records for all screened patients until 2011. More specific medical information regarding the included women was retrieved from the same sources and registered on clinical research forms (CRFs) by a research nurse. The CRFs contained data on demographics, physical performance status, and the results of a physical examination including length, weight, BMI, and blood-pressure as well as patient-reported information on present medications including hormonal treatments, pre-/postmenopausal status, details on the menstrual cycle, and smoking habits including date of smoke stop.

In study IV, additional information on radiological assessments of MRI examinations were retrieved through medical records from Ersta hospital, where RC patients were followed annually with MRI as part of routine follow-up after treatment. The possibility to re-evaluate all follow-up CT-scans was considered and discussed with an expert in diagnostic radiology but the idea was abandoned due to logistic reasons.

Questionnaires on patient reported outcome measures, PROMs

The participants completed the questionnaires at outpatient visits at baseline and one year after surgery. Two years postoperatively, the questionnaires were sent and returned by post.

Female Sexual Function Index (FSFI)

To evaluate sexual function, the FSFI questionnaire was used. The questionnaire is described in detail in *Background* and shown in the Swedish translation below in Appendix 1.

Psychological General Well-being Index (PGWBI) (Appendix 2)

The PGWBI is a well-established tool used in cancer patients, post-menopausal women, and other cohorts (252). According to previous studies, female sexual function is closely related to psychological well-being (253). Associations between androgens and specific aspects of psychological well-being have been suggested; however, results are contradictive (190, 200, 254, 255). Therefore the PGWBI was included in the analyses of Study II and III. The questionnaire comprises 22 items divided into six domains: anxiety, depressed mood, positive well-being, self-control, general health, and vitality. The domain scores are added and weighted into scores 0–100; a higher score means better psychological status (256, 257).

Participants were asked to answer the questionnaires FSFI and PGWBI according to their functional status before the first disease symptoms or date of diagnosis in case of asymptomatic disease.

Bowel and urinary function (Appendix 3)

The Modified Miller score was introduced in *Background*. In the present study, three questions were added: Q1: stoma at present (yes, no), Q5 and Q6: anchoring questions about impact on quality of life from urinary and bowel problems, respectively.

Laboratory data

Blood samples were drawn at baseline, the day before surgery (only participants treated with RT) and one year postoperatively. At each time point, serum was stored for later analyses of T, A-4, DHEAS, oestradiol, FSH, LH, Sex hormone binding globulin (SHBG), albumin, sclerostin, CTX-1, BALP, and intact PINP. Routines regarding sampling, storage and analytic methods are closely described in the separate studies; androgens in Study I, Appendix 1 and in brief in Study III; FSH and AMH in Study III, and bone biomarkers and oestradiol in Study IV Appendix A. Free T was calculated using a multistep model based on testosterone's binding to SHBG (258, 259).

5.3 STUDY V

5.3.1 Participants and data sources

Definition of cohort 1, Swedish oncologists, surgeons and oncology specialty trainees treating RC in the preceding three years, identified through national specialty associations, and the regional directors of studies of the national oncology specialisation programme. All who agreed to participate were included in the study.

Definition of cohort 2, RC patients having undergone abdominal surgery in the Stockholm-Gotland health care region, diagnosed between 1 April 2017 to 31 July 2020, and identified through the Swedish Colorectal Cancer Registry. Patients operated at Karolinska University Hospital and Ersta Hospital were excluded, as these centres ran a dedicated programme for functional rehabilitation. Further, patients who did not answer any of the items of interest in study V were excluded from the analysis.

5.3.2 Questionnaires, invitation, and data collection

Cohort 1, The web-based questionnaire included 24 (item 2–25) items exploring the extent to which the physician inform about sexual side effects, barriers to information, self-assessed subject knowledge level, educational needs, and general data on the respondents' characteristics. Item 1 asked for informed consent to participate in the study. The questionnaire was developed by the authors and the items were similar to those used in previous Dutch studies among surgeons and oncologists but adjusted to match the research aims, and in line with recommendations on survey construction. The invitation was sent to the population of interest with an invitation to reply to an anonymous web-based survey. The email included study information, a link to the survey, and a request to be forwarded to colleagues outside the specialty associations although active in RC treatment. A reminder was sent after two to three weeks to all recipients.

Cohort 2, The patient questionnaire was part of an evaluation addressing functional outcomes after RC treatment. In study V, four items regarding information and counselling of sexual side effects were analysed. The questionnaire was sent by mail 18–22 months after resection of the primary tumour, and sent a second time to non-responders. Non-responders to the reminder were contacted by phone by a research nurse. Informed consent was obtained from all participants. Information on patients' clinical characteristics were retrieved from the Swedish Colorectal Cancer Registry

5.4 STATISTICS

Cross-sectional analyses

In study I, II, and IV, Fisher's exact test and Wilcoxon's rank sum test were used for categorical and continuous variables, respectively, in comparisons between RT-exposed and unexposed groups at each time-point for a descriptive purpose.

In study V, cohorts 1 and 2 were analysed separately and no statistical comparisons between the two cohort was planned. Categorical variables were presented with counts and frequencies and continuous variables with median (range). For comparison between groups of physicians or patients, Pearson's chi-squared, Fisher's exact, and McNemar's tests were used for proportions and Wilcoxon's rank sum test for median values. Uni- and multivariable logistic regression were applied to explore the importance of the physicians' and the patients' characteristics for the degree of information provided and received, respectively. The participants in cohort 1 were allocated into two groups ('high' and 'low') depending on the reported degree and content of information provided (items 2-5), and the participants in cohort 2 were allocated into two groups according to whether they recalled having received information before treatment or not.

Longitudinal analyses

Generalized estimation equation (GEE) models were used to estimate the difference in change over time of dependent variables (study I, androgens; study II, FSFI scores, and study IV, bone biomarkers) between treatment-groups and other tested independent variables. Generalized lest squares (GLS) regression models with random-effects, were used to evaluate associations between androgens and sexual function in study III. In the crude analysis, McNemar's test and Wilcoxon's signed-rank test were applied for longitudinal within-group comparisons of categorical and continuous variables, respectively.

5.5 ETHICAL PERMITS

All studies were conducted in agreement with the Declaration of Helsinki (260) and ethical approvals were obtained as listed below.

The studies I–IV

Dnr 2008/247-31/3, and listed amendments:
Dnr 2009/1988-32: Additional including hospital
Dnr 2009/622-32: Additional including hospital
Dnr 2012/1730-32/3: Increased number of study participants and additional of 2 years follow-up PROMs (FSFI, PGWBI,–Modified Miller Score)
Dnr 2020-02148 - review of medical records

Study V:

Dnr 2022-00971-01; Dnr 2018/1889-3

6 RESULTS

6.1 COHORT STUDY – FEMALE SEXUAL FUNCTION AND WELL-BEING IN RECTAL CANCER

Enrolment in study and lost to follow-up from baseline to two-years follow-up

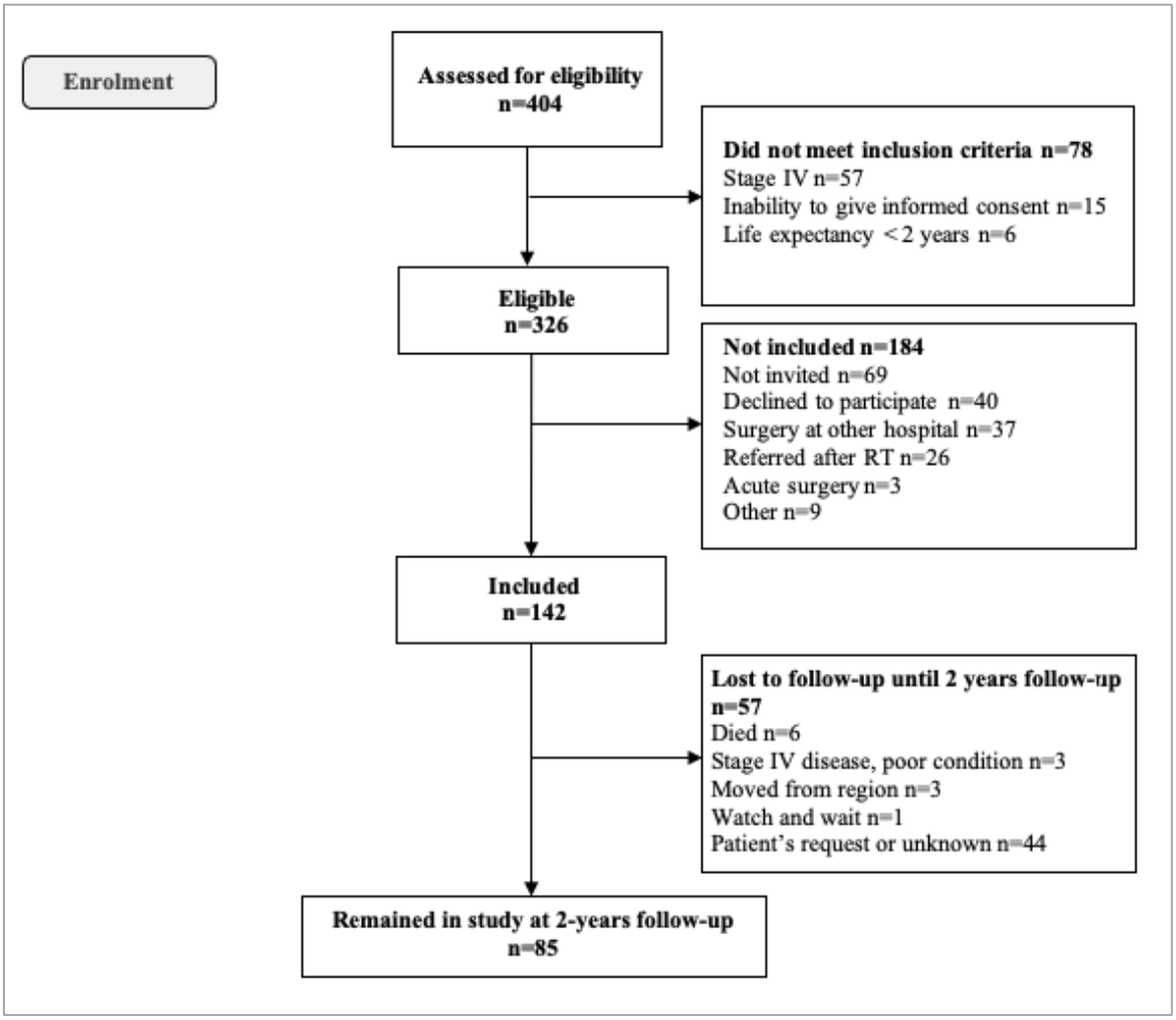

Figure 11
Enrolment of participants for study I–IV. Lost to follow-up at 2-years follow

In all, 404 females were screened for inclusion, of whom 78 did not meet the inclusion criteria, leaving 326 patients eligible for inclusion. Of these, 184 were not included for reasons listed in *Figure 11*. Among the 142 included participants, 110 were treated with RT and 32 were not. One-hundred and twenty-one and 85 females were followed for one and two years postoperatively, respectively. Table 3 shows baseline characteristics by treatment group: preoperative RT (RT+) or surgery alone (RT-). Patients treated with RT were younger (median age 62 versus 69.5 years, $P<0.001$) with a trend to lower rectal tumours

(*P*=0.080) than patients treated with surgery alone. No significant differences were seen regarding pathological tumour stage.

Table 3 Participant and tumour characteristics

	All included N=142	RT+ N=110	RT- N=32	Cross-sectional comparison*
Age (years)	63 (26–90)	62 (26–81)	69.5 (46–90)	0.001
BMI (kg/m^2)	24 (17–40)	24 (17–37)	24 (18–40)	0.199
Smoking				1.000
Yes	16 (11)	13 (12)	3 (10)	
No	73 (52)	57 (52)	16 (52)	
Former	52 (37)	40 (36)	12 (39)	
ASA score				0.193
I	43 (31)	35 (32)	8 (26)	
II	73 (52	59 (54)	14 (45)	
III	25 (18)	16 (15)	9 (29)	
pTNM				0.630
0	11 (8)	10 (9)	1 (1)	
I	34 (25)	24 (22)	10 (32)	
II	35 (25)	29 (27)	6 (19)	
III	52 (38)	39 (36)	13 (42)	
IV (after incl.)	6 (4)	4 (5)	1 (3)	
Tumour distance from anal verge (cm)				0.080
0–4	50 (35)	46 (42)	4 (12)	
5–10	55 (39)	40 (36)	15 (47)	
11–15	37 (26)	24 (22)	13 (41)	

Values are presented as median (range) and numbers (percentage) for continuous and categorical values, respectively. *Wilcoxon's rank-sum test and Fisher's exact test for continuous and categorical values, respectively. RT, radiotherapy; BMI, body mass index; ASA, American Society of Anaesthesiologists; pTNM, pathological tumour-nodes-metastases stage.

An interim analysis was performed after the inclusion of the first 82 of 157 eligible females in 2013 to compare patient characteristics between eligible included and non-included females and between participants with different response patterns in the FSFI. Included patients were younger and had better physical status (ASA score) than non-included patients. The proportion who had a partner was significantly higher among females who completed all FSFI domains than among those who did not (49 of 57 (86%) *vs* 7 of 25 (28%), *P*=0.001) (250).

Table 4 shows baseline number of participants with FSH levels ≤ 25 and > 25 units/L, respectively, and the number who had ongoing hormone replacement therapy in the RT+ and RT- groups. A serum level of FSH > 25 units/L was considered to indicate postmenopausal status, being the lower limit of the FSH reference value in menopause in the laboratory method used by the Karolinska University Laboratory at the time of analysis. Lower levels are seen in females on hormone replacement therapy. In females treated with RT, the proportion with FSH > 25 units/L increased significantly after RC treatment (not in the table).

Table 4 Follicle-stimulating hormone (FSH) levels indicating menopause at baseline and hormone replacement therapy, by group

	All included N=142	RT N=110	No RT N=32	Cross-sectional comparison (*P**)
FSH > 25 units/L baseline				0.565
Yes	119 (87)	91 (86)	29 (91)	
No	18 (13)	14 (14)	3 (9)	
Missing	5	5	-	
HRT, systemic effect				-
Baseline	9 (6)	8 (7)	1 (3)	
1-year follow-up	7 of 121 (6)	7	0	

Values represent counts (frequency). *Fisher's exact test. RT, radiotherapy; HRT, hormone replacement therapy.

Rectal cancer treatment

Data on oncological and surgical treatment are shown in Table 5. Radiotherapy was delivered in accordance with Swedish guidelines, with a predominance of the short-course schedule. Most CRT schedules were standard, i.e. long-course RT with concomitant peroral capecitabine or intravenous bolus FLv, and four patients had sequential treatment within the experimental arm of the RAPIDO trial (86). Radiotherapy was delivered with 'box technique' with few exceptions. Two patients underwent IMRT or VMAT. Patients included in the very beginning of the study period were treated without prior delineation of the target. There was a gradual implementation of target delineation and 3D-conformal treatment with the use of multi-leaf collimators. Abdominoperineal resection (APR) was more common in the RT+ than the RT- group (54 of 110 (50%) versus 8 of 30 (27%), p=0.037).

Table 5
Oncological and surgical treatment in patients with preoperative RT (RT+) and surgery alone (RT-)

	All included N=142	RT+ N=110	RT- N=32	Comparison RT+ vs RT-
Preoperative (C)RT				
5 Gy x 5, direct surgery		49 (45)		
5 Gy x 5, delay		20 (18)		
5 Gy x 5, delay + chemo		4 (4)		
1.8–2.0 Gy x 25–28		6 (6)		
CRT 1.8–2.0 Gy x 25–28		31 (28)		
Radiation technique[+]				
Box[++]		88		
IMRT or VMAT		2		
Abdominal surgery				0.037
AR	76 (55)	54 (50)	22 (73)	
APR including Hartmann	62 (45)	54 (50)	8 (27)	
Intersphincteric	6 (4)	3 (3)	3 (9)	
Conventional	24 (17)	21 (19)	3 (9)	
Extralevator	30 (21)	29 (26)	1 (3.1)	
Hartmann	2 (1)	1 (1)	1 (3.1)	
No abdominal surgery	4 (3)	2 (2)	2 (6.3)	-
Gynaecological resections *				
Hysterectomy	18	13 (11.8)	5 (18.8)	0.531
Uni-/Bilateral oophorectomy	20	16 (11.2)	4 (2.8)	1.000
Partial vaginal resection	9	9	0	0.205
Adjuvant chemotherapy	45 (32.1)	36 (33.3)	9 (28.1)	0.670

Values are numbers (%). Fisher's exact test used for comparisons. [+]Data only for patients treated in Stockholm. Seven treatment plans were fields based on landmarks. [++]Seventy-eight were 4-field. *Numbers include resections before study inclusion and as part of RC surgery. RT, radiotherapy; CRT, chemoradiotherapy; IMRT, intensity modulated RT; VMAT, volumetric modulated arch therapy; AR, anterior resection; APR, abdominoperineal resection.

Psychological well-being

The PGWBI total scores (range 0–100) did not change significantly within the two treatment groups during the study and were similar between groups at baseline (72.7 (range 20–95.5) in RT+ and 71.8 (35.5–94.5) in RT- (p=0.763) and at follow-up (median value 72.7 vs 77.3 (*p*=0.200) after one year and 75.0 vs 72.7 (*p*=0.790) after two years. PGWBI total score was a significant predictor of sexual function in Studies II and III. Domain scores (not previously published) are shown in Table 6. Anxiety improved from baseline to one year in the RT- group and differed between groups at one year.

Table 6.
Psychological General Well-Being Index (PGWBI) domain scores in RT+ and RT- groups.

PGWBI domain scores	RT-			RT+			
	Median (range)	N	Longitudinal comparison *P*	Median (range)	N	Longitudinal comparison *P*	Cross-sectional *P*
Anxiety							
Baseline	72.0 (32.0-96.0)	30		72.0 (8.0-100.0)	106		(0.848)
1 year	84.0 (48.0-100.0)	25	(0.014)	76.0 (16.0-100.0)	90	(0.461)	(0.024)
2 years	80.0 (20.0-100.0)	17	(0.243)	80.0 (16.0-100.0)	65	(0.607)	(0.752)
Depression							
Baseline	86.7 (33.3-100.0)	30		80.0 (33.3-100.0)	106		(0.401)
1 year	86.7 (73.3-100.0)	26	(0.152)	86.7 (26.7-100.0)	91	(0.773)	(0.037)
2 years	86.7 (40.0-100.0)	17	(0.792)	86.7 (33.3-100.0)	67	(0.885)	(0.401)
Positive well-being							
Baseline	57.5 (25.0-85.0)	30		65.0 (15.0-95.0)	106		(0.998)
1 year	65.0 (40.0-95.0)	25	(0.277)	60.0 (15.0-100.0)	90	(0.428)	(0.456)
2 years	60.0 (25.0-80.0)	17	(0.882)	60.0 (25.0-100.0)	65	(0.511)	(0.945)
Self-control							
Baseline	86.7 (33.3-100.0)	30		86.7 (13.3-100.0)	106		(0.861)
1 year	93.3 (60.0-100.0)	25	(0.092)	86.7 (6.7-100.0)	90	(0.783)	(0.070)
2 years	86.7 (13.3-93.3)	17	(0.867)	86.7 (26.7-100.0)	65	(0.706)	(0.727)
General health							
Baseline	66.7 (20.0-100.0)	30		70.3 (20.0-100.0)	106		(0.409)
1 year	66.7 (20.0-100.0	26	(0.750)	80.0 (0.0-100.0)	91	(0.997)	(0.663)
2 years	73.3 (33.3-100.0)	17	(0.775)	80.0 (20.0-100.0)	67	(0.326)	(0.353)
Vitality							
Baseline	62.5 (20.0-100.0)	30		70.0 (10.0-100.0)	106		(0.310)
1 year	65.0 (50.0-90.0)	25	(0.181)	67.5 (20.0-100.0)	90	(0.625)	(0.721)
2 years	60.0 (20.0-90.0)	17	(0.633)	65.0 (15.0-100.0)	65	(0.673)	(0.713)

Longitudinal and Cross-sectional comparisons with Wilcoxon's Signed rank Rank-sum test, respectively.

Bowel function at two-year follow-up

Bowel function according to the Modified Miller score was measured in 85 females at two-years follow-up, of whom 67 were treated with RT and 18 were not (Table 7). Nineteen of 85 participants experienced that bowel problems affected their sexual relations ‘quite a bit’ or ‘a lot’. Median Modified Miller scores for patients in the RT+ and RT- group corresponded to grade II incontinence for flatus. The RT- groups had no incontinence for solid stools and lower scores for incontinence of liquid stools than the RT+ group. In the latter, some patients experienced incontinence for solid stools.

Table 7
Bowel function

	All participants N, 85	RT+ N, 67	RT- N, 18	Comparisons between groups, *P*
Impact of bowel problems on sexual relation, N (%)				
Not at all	14 (16)	11 (16)	3 (17)	
A little	13 (15)	9 (13)	4 (22)	
Quite a bit	4 (4)	4 (6)	-	
A lot	15 (18)	13 (19)	2 (11)	
Not relevant	37 (44)	29 (43)	8 (44)	
Missing	2 (2)	1 (2)	1 (6)	
Impact of urinary problems on sexual relation, N (%)				
Not at all	37 (44)	30 (45)	7 (39)	
A little	5 (6)	3 (5)	2 (11)	
Quite a bit	3 (4)	2 (3)	1 (6)	
A lot	1 (1)	1 (2)	-	
Not relevant	38 (45)	31 (46)	7 (39)	
Missing	1 (1)	-	1 (6)	
Modified Miller score, participants without stoma**,** median (IQR)	N, 43	N, 30	N, 13	
Total, range 0–18	7 (1–12)	7 (2–14)	3 (1–8)	
Flatus, range 0–3	2 (1–3)	2 (1–3)	2 (1–3)	
Liquid, range 0–6	4 (0–5)	4 (0–5)	0 (0–4)	
Stools, range 0–9	0 (0–7)	0 (0–7)	0 (0–0)	
Sexual function and in stoma groups	**All** N, 85	**Stoma** N, 42	**No stoma** N, 43	
FSFI total, median (IQR)	8.3 (3.6–18.2)	6.4 (2.6–16.7)	11.1 (3.6–18.5)	0.376*
Missing, N	19	13	6	

*Wilcoxon’s rank sum test. RT, radiotherapy; IQR, interquartile range; FSFI, Female Sexual Function Index;

Modified Miller score, grading system:

	Flatus	Liquid stool	Solid stool
Never	0	0	0
Grade I. Incontinence episodes occasionally. (<once /week – once/month)	1	4	7
Grade II. Incontinence at least once per week. (< once /day – once /week)	2	5	8
Grade III. Incontinence daily (≥ once /day)	3	6	9

Lost to follow-up

Fifty-seven of the 142 participants (40%) were lost to follow-up from baseline to two-year follow-up. A comparison of the baseline and treatment characteristics and main baseline outcome variables in studies I–III revealed no statistically significant differences between groups, except for a higher median age among women who were lost to follow-up (Table 8). Different reasons for being lost to follow-up are listed in Figure 11.

Table 8 Analysis of lost to 2-years follow-up.
Baseline and treatment characteristics and baseline main outcome variables are compared between participants remaining in the study *vs* being lost to follow-up.

	Remain in study N (%)	**Lost to follow-up** N (%)	**Comparison** *p*-value
N, all: 142	85	57	
Age, median years (range)	63 (26–80)	65 (32–90)	0.162
Had a partner	59 (69)	39 (65)	0.712
Missing	1	2	
ASA classification			0.163
I	26 (31)	17 (30)	
II	48 (56)	25 (44)	
III	11 (13)	14 (25)	
Missing	-	1 (2)	
pTNM			0.347
0	9 (11)	2 (4)	
I	19 (22)	15 (26)	
II	23 (27)	12 (21)	
III	32 (38)	20 (35)	
IV (after incl.)	2 (2)	4 (7)	
Missing	-	4 (7)	
Preoperative (C)RT	67 (79)	43 (75)	0.685
Type of surgery			1.000
Anterior resection	47 (55)	29 (55)	
Abdominoperineal resection*	38 (45)	24 (45)	
Other**	-	4 (6)	
Neoadjuvant chemotherapy	21 (25)	15 (26)	0.846
Adjuvant chemotherapy	26 (31)	19 (33)	0.712
Missing	-	2 (4)	
FSFI total score, median (range)	18.9 (2–36)	14.4 (2–32.3)	0.729
Missing, N (%)	15 (18)	13 (23)	
PGWBI score, median (range)	74.5 (20–95.5)	69.5 (28.2–94.5)	0.654
Missing, N (%)	2 (2)	1 (2)	
Testosterone, median (range)	0.7 (0.1–4.8)	0.6 (0.1–2)	0.707

Wilcoxon rank sum and Fisher's exact test and was used for comparison of continuous and categorical variables, respectively. * Six intersphincteric, 24 conventional, and 30 extralevator APR, and 2 Hartmann's procedure. ** Four transanal resections. ASA, American Society of Anaesthesiologists' physical classification (I–IV); pTNM, pathological tumour-nodes-metastases stage; (C)RT, chemoradiotherapy; FSFI, Female Sexual Function Index; PGWBI, Psychological General Well-being Index. Number of missing not indicated means no missing data.

6.2 STUDY I

Seventeen of 142 females had a history of oophorectomy. The remaining 125 were included in this study. Eleven females in the RT+ group and one in the RT- group underwent oophorectomy concomitantly with the operation of the primary tumour, and were excluded from further analyses. In the crude analysis, serum levels of all four measured androgens decreased significantly in the RT+ group during the study, and only DHEAS decreased in the RT- group. Regression analysis, illustrated by the graphs in *Figure 12*, showed a significant associations between RT and decrease in T and free T.

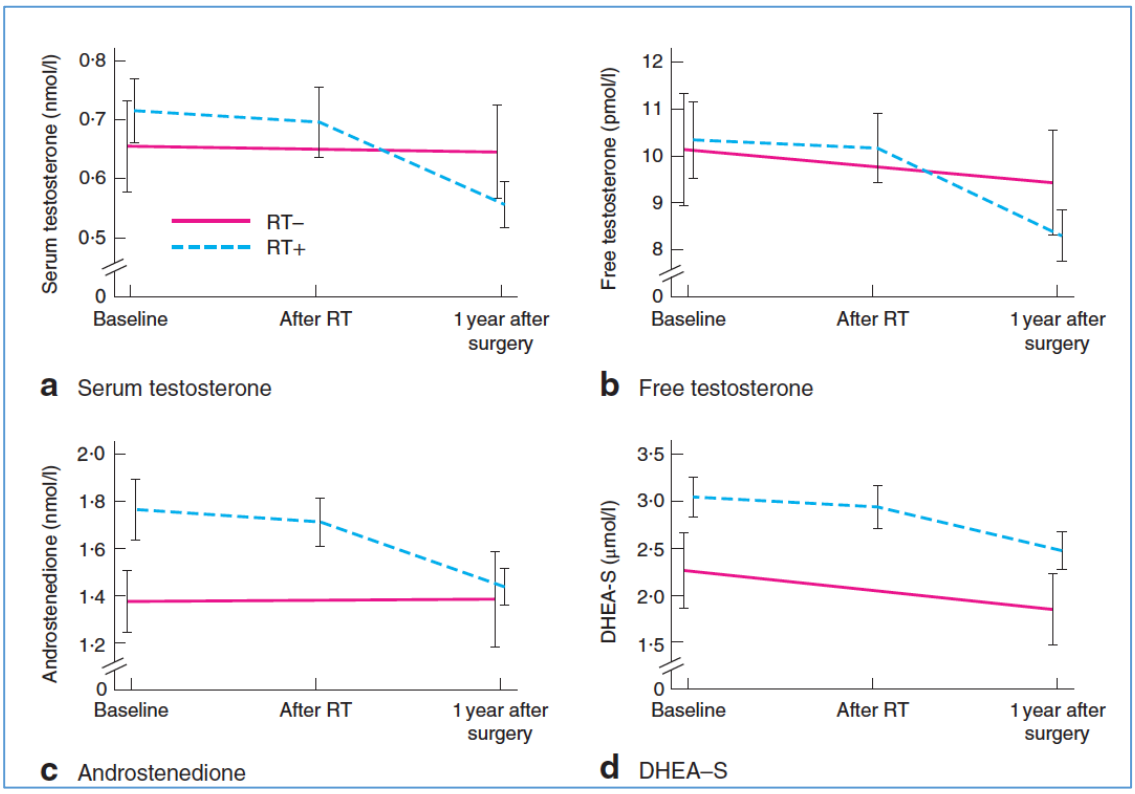

Figure 12. (261)*:* Mean (standard deviation) androgen levels over time in the surgery-alone (RT-) and preoperative radiotherapy and surgery (RT+) groups: **a** serum testosterone **b** free testosterone (P=0.028 for the estimate of RT+), **c** androstenedione, **d** dehydroepiandrosterone sulfate (DHEAS). RT, radiotherapy.

The odds ratio of a score indicating normal *vs* low sexual desire increased with increase in T, free T and A-4 , and with decrease in DHEAS (Table 9).

Table 9
Association between change in androgen levels and sexual desire

	Odds ratio	*P*
Serum testosterone*	2.74 (1.06, 7.11)	0.038
Free testosterone†	1.08 (1.02, 1.15)	0.011
Androstenedione*	1.52 (1.07, 2.16)	0.019
DHEAS‡	0.49 (0.27, 0.89)	0.019

Values in parentheses are 95 percent confidence intervals. Scores for sexual desire were dichotomised on the 75th percentile at baseline. *Adjusted for follicle-stimulating hormone (FSH); †adjusted for FSH and body mass index; ‡interaction with FSH and adjusted for body mass index. DHEAS, dehydroepiandrosterone sulfate.

6.3 STUDY II

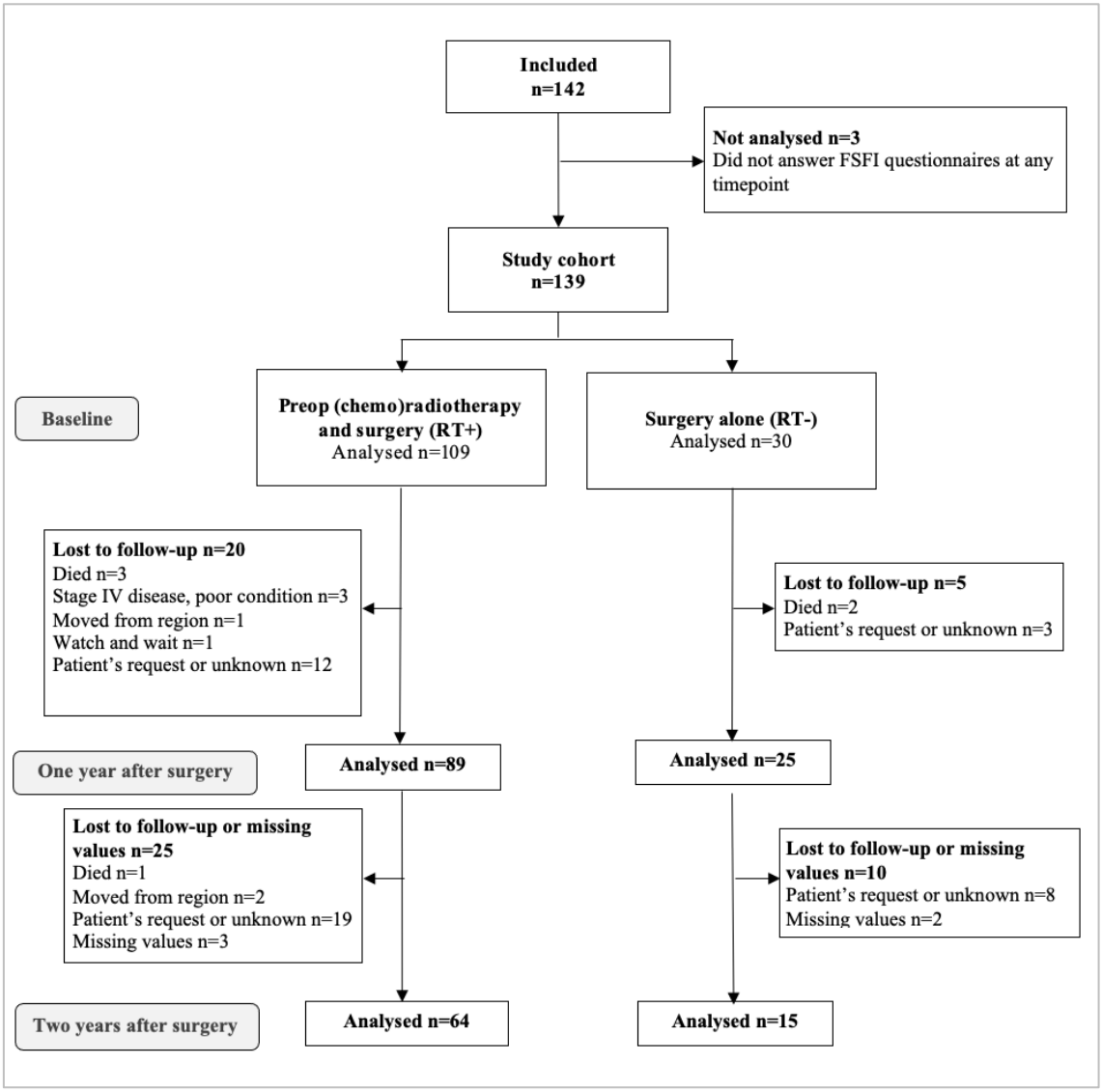

Figure 13
Enrolment of participants for study I–IV. Lost to follow-up at 2-years follow

The entire cohort and sexually active females were studied separately. *Sexual activity* was defined as an absence of the response options *no sexual activity* or *did not attempt intercourse* in at least one FSFI domain including these options (N=99). The median FSFI total score of all participants decreased from 18.5 at baseline to 10.8 two years postoperatively in the RT+ group. The baseline score in the RT- group was 6.7 and did not decrease during the study. The proportion of sexually active females at baseline did not differ significantly between the treatment groups (P=0.624). Baseline values were higher among sexually active participants in both treatment groups. The graphs below represent results of the multivariable regression analysis (*Fig. 14 and 15*). Radiotherapy was associated with a decline in FSFI total score and sexual arousal, lubrication, orgasm, and pain, in all patients. In sexually active females, associations were present with total FSFI,

sexual desire, arousal, and pain and close to significant in lubrication and orgasm. Other predictors of sexual function were age, partner (yes/no), and psychological well-being, adjusted for in the multivariable analysis.

The ovarian reserve was assessed with AMH and analysed in the nine premenopausal females aged 45 years or younger, of whom six had detectable values at baseline. All six received RT with an equal number of short- and long-course schedules, and none had detectable values at one-year follow-up.

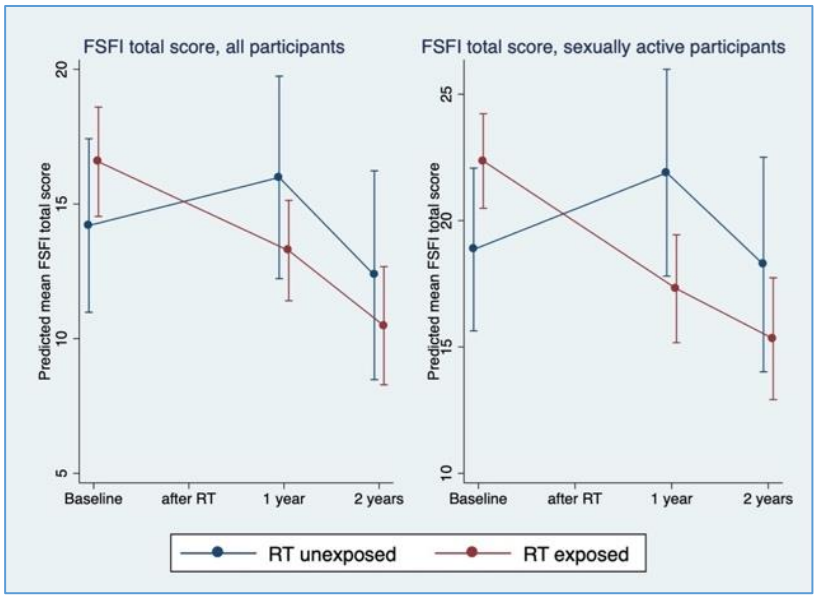

Figure 14. Results of the multivariable analysis. The graphs show change in FSFI total score among all included participants (left), p=0.013 and sexually active (right), p=0.002, compared between RT+ and RT- (4).
FSFI, Female Sexual Function Index; RT, radiotherapy.

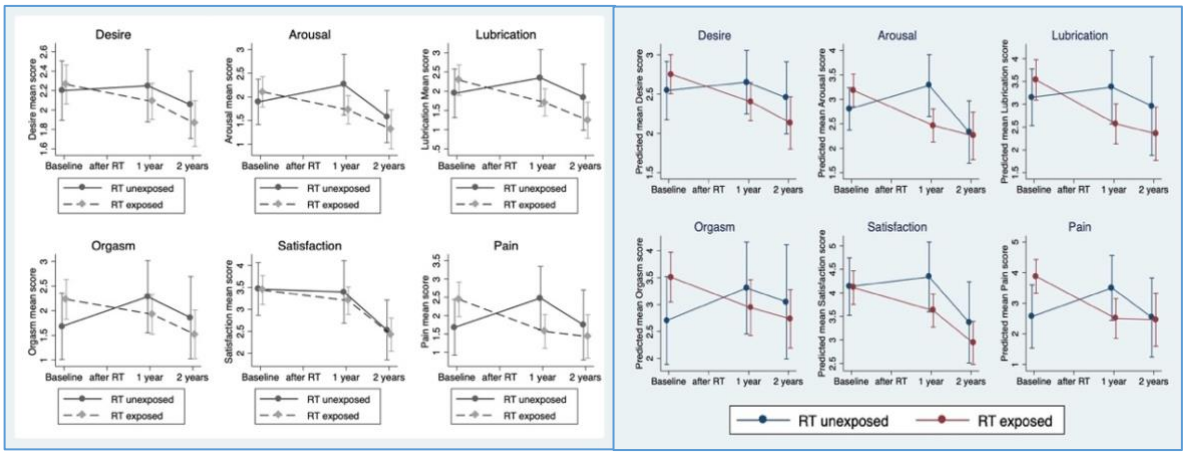

Figure 15. Results of the multivariable analysis. Change in Female Sexual Function Index domain scores for all participants (left) and sexually active participants (4) (right), compared between RT+ and RT- Adjustments were made for age, psychological well-being and partner. RT, radiotherapy.

Errata: In the published version of Study II, an error in numbers occurred regarding the two-year follow-up (Figure 1, published version). The correct numbers are displayed in *Figure 13* (above). Further, there were no missing values at one or two years regarding the variable partner (yes/no) and PGWBI total score, which was incorrectly typed in Table 3, published article (262).

6.4 STUDY III

Ninety-nine sexually active participants were included and assessed for associations between androgens and sexual function. Twelve were premenopausal at baseline. Seventy-nine (80%) had preoperative RT, 42 (42%) were operated on with APE and eight (8%) had partial vaginal resection during RC surgery.

Table 10
Androgen levels at baseline and one year postoperatively

	Baseline	1 year	Longitudinal comparison *P**
N, total	99	99	
Testosterone (nmol/L)	0.6 (0.1–3.6)	0.5 (0.1–2.3)	0.005
N	99	85	
Free testosterone (pmol/L)	8.7 (1.6–45.8)	7.7 (1.4–22.7)	0.021
N	99	83	
Androstenedione (nmol/L)	1.6 (0.3–7.8)	1.4 (0.3–4.4)	0.100
N	98	85	
DHEA (µmol/L)	2.9 (0.2–9.0)	2.4 (0.1–8.4)	<0.001
N	97	83	

Values are presented as median, range. *Wilcoxon's signed-rank test. DHEAS, dehydroepiandrosterone sulfate.

The androgen levels were measured at baseline, the day before surgery (RT+ group), and one year postoperatively and assessed for associations with FSFI scores. The total FSFI score decreased from 21.9 at baseline to 16.4 and 11.5 at the one- and two-year follow-up, respectively (not shown in table). In unadjusted longitudinal analysis, there was a statistically significant decline in androgens other than A-4 (Table 10).

Table 11
Multivariable regression analysis of androgens and sexual function

	FSFI Total	Desire	Arousal	Lubrication	Orgasm	Satisfaction	Pain
	estimate 95% CI *P*	estimate 95% CI *P*	estimate 95% CI *P*	estimate 95% CI *P*	estimate 95% CI *P*	estimate 95% CI *P*	estimate 95% CI *P*
Testosterone (nmol/L)	3.45 0.92–5.97 0.008	0.30 -0.02–0.62 0.064	0.40 -0.01–0.82 0.059	0.80 0.26–1.33 0.003	0.80 0.12–1.48 0.021	0.35 -0.13–0.83 0.155	0.63 -0.11–1.37 0.093
Free testosterone (pmol/L)	0.16 -0.04–0.36 0.120	0.01 -0.01–0.04 0.383	0.02 -0.01–0.06 0.209	0.04 0.00–0.09 0.045	0.04 -0.01–0.09 0.128	0.01 -0.03–0.05 0.633	0.26 -0.03–0.08 0.368
Androstenedione (nmol/L)	1.39 0.46–2.33 0.004	0.06 -0.06–0.17 0.349	0.27 0.10–0.44 0.002	0.44 0.26–0.63 <0.001	0.30 0.04–0.55 0.024	0.11 -0.07–0.29 0.229	0.43 0.14–0.72 0.004
DHEAS (µmol/L)	0.36 -0.39-1.11 0.343	-0.01 -0.10-0.08 0.849	0.04 -0.11-0.18 0.603	0.09 -0.08-0.27 0.296	0.05 -0.13-0.23 0.559	0.03 -0.08-0.13 0.607	0.14 -0.07-0.35 0.196

FSFI, Female Sexual Function Index; CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate.

In the multivariable regression analysis (Table 11), total T and A-4 were associated with total FSFI and the two domains of lubrication and orgasm. A-4 was further associated with sexual arousal and dyspareunia, free T with lubrication, and DHEAS with none of the domains. Adjustments were made for the following patient- and treatment-related factors: age, psychological well-being, partner, RT and type of surgery.

6.5 STUDY IV

This study included all participants with available serum samples for bone biomarker analysis from any timepoint during the study (N=134). Within group analysis of change in bone biomarkers were analysed in all participants from baseline to one-year follow-up and from baseline to the day before surgery in the RT+ group. The bone formation markers BALP decreased significantly from baseline to the day before surgery in the RT+ group and increased in BALP and PINP from baseline to one-year follow-up (Table 12).

Table 12
Comparisons of levels of bone biomarkers between RT+ and RT- groups, and changes within groups.

	RT-exposed			RT-unexposed			
	N	**Serum level**	**Longitudinal comparison* *P*[a]**	**N**	**Serum level**	**Longitudinal comparison* *P*[a]**	**Cross-sectional comparison *P*[b]**
Sclerostin (pmol/L)							
Baseline	87	37.6 (13.9–104.1)		26	39.7 (3.2–110.1)		0.833
After RT	80	34.8 (13.22–88.8)	0.216	-	-	-	-
1 y	87	37.3 (9.0–122.4)	0.238	24	45.2 (3.2–92.3)	0.161	0.174
CTX (ng/mL)							
Baseline	87	0.16 (0.03–0.45)		26	0.17 (0.02–0.40)		0.487
After RT	80	0.17 (0.04–0.67)	0.432	-	-	-	-
1 y	87	0.19 (0.04–0.77)	0.068	24	0.18 (0.05–0.37)	0.433	0.437
BALP (U/L)							
Baseline	87	12.8 (5.1–53.3)		26	11.9 (3.2–33.7)		0.604
After RT	80	12.2 (6.1–25.6)	0.011	-	-	-	-
1 y	87	15.9 (6.0–38.2)	<0.001	24	12.2 (2.2–26.8)	0.391	0.082
Intact PINP (µg/L)							
Baseline	87	52.0 (10.6–127.0)		26	43.6 (8.5–115.5)		0.227
After RT	80	49.7 (16.1–157.2)	0.826	-	-	-	-
1 y	87	64.3 (17.5–239.0)	<0.001	24	51.1 (18.5–97.0)	0.391	0.006

Values are median (range) for bone biomarkers. Longitudinal measures are calculated with [a]Wilcoxon's signed-rank test and cross-sectional comparisons between groups with [b]Wilcoxon's rank-sum test. *Values after RT and at 1-year follow-up are compared with baseline. RT, radiotherapy; CTX, carboxy-terminal cross-linking telopeptide of type I collagen; BALP, bone-specific alkaline phosphatase; PINP, amino-terminal propeptide of type I procollagen.

According to the multivariable analysis (Table 13), adjusted for age, serum oestradiol, and adjuvant chemotherapy, the difference in the mean increase in PINP until one year was associated with RT (17.58 (3.64–31.51) µg/L, *P*=0.013). The corresponding result for BALP was not statistically significant (1.66 (-0.31–3.79) U/L, *P*=0.097). The mean change

in the bone resorption marker CTX and the regulating protein sclerostin did not change significantly in the RT+ compared with the RT- groups.

Table 13
Multivariable analysis comparing changes in bone biomarkers between RT-exposed and unexposed participants

		Sclerostin (pmol/L)	**CTX** (ng/mL)	**BALP** (U/L)	**PINP** (μg/L)
N=130		Estimates 95% CI *P*-value	Estimates 95% CI *P*-value	Estimates 95% CI *P*-value	Estimates 95% CI *P*-value
Multivariable[+] Reference group: RT-	Day before surgery	-1.69 -4.34 to 1.00 0.221	0.01 -0.02 to 0.04 0.534	-1.04 -2.22 to 0.13 0.083	1.33 -5.04 to 7.71 0.682
	1 year after surgery	-2.09 -7.02 to 2.83 0.404	0.02 -0.04 to 0.08 0.578	1.66 -0.31 to 3.79 0.097	17.58 3.64 to 31.51 0.013
	Entire study period*	-3.76 -9.66 to 2.14 0.211	0.03 -0.05 to 0.10 0.486	0.69 -1.99 to 3.38 0.612	18.91 2.62 to 35.20 0.023

Generalised estimating equations models were used for analysis. The estimates represent the mean difference in mean change in bone biomarkers over time between RT-exposed and unexposed. *Entire study period includes changes in values from baseline to the day before surgery and one year after surgery, added up by linear combination in the regression model. [+]Adjusted for age, serum-oestradiol, and adjuvant chemotherapy. RT, radiotherapy; CTX, carboxy-terminal cross-linking telopeptide of type I collagen; BALP, bone-specific alkaline phosphatase; PINP, amino-terminal propeptide of type I procollagen; CI, confidence interval.

Forty-nine females were assessed for signs of RT-induced bone damage. Their MRI assessments were reviewed. There were signs of RT-induced pelvic bone damage in 16 of these of participants. The bone damage was all identified within three years postoperatively, and 11 of 16 occurred within one year. There were no significant differences between patients with and without radiation injury regarding baseline characteristics (age, BMI, smoking, ASA score) or exposure to chemotherapy. The median value of the bone formation biomarker BALP was higher in the group with bone damage than in the other group after one year (16.0 (95% CI 10.0–30.8) *vs* 13.3 (8.7–22.6) *P*=0.018, cross-sectional comparison). Due to the small number of participants in the comparison groups (with *vs* without bone damage), longitudinal regression analysis for assessing associations between bone damage and change in bone biomarkers was not performed.

6.6 STUDY V

The web-based questionnaire was sent to 591 physicians and forwarded to an unknown number who were not members of specialty associations. One hundred eighty-six consented to participation (first item), and 166 completed all items. The clinical experience differed between surgeons and oncologists. Sixty-nine (87%) *vs* 30 (35%) were senior consultant physicians, 10 (13%) *vs* 14 (16%) were junior consultants physicians, and none *vs* 43 (49%) were specialty trainees ($P<0.001$) (not shown in table).

Table 14
Characteristics of physicians (cohort 1) and logistic regression for the odds of informing to a 'high' degree about adverse sexual side effects before curative treatment.

	Informed to a low degree N (%) 122 (69.7)	Informed to a high degree N (%) 53 (30.3)	Logistic regression (informing to a high *vs* low degree) Odds ratio (95% confidence interval)	
			Univariable	Multivariable
N, completed all items, 166	114 (68.7)	52 (31.3)		
Age (years)				NA*
< 40	36 (31.6)	8 (15.4)	(ref)	
40–55	57 (50.0)	27 (51.9)	2.13 (0.87–5.20)	
> 55	21 (18.4)	15 (28.9)	3.21 (1.17–8.85)[+]	
Not specified	0	2 (3.9)	NA	
Missing	8	1	NA	
Gender				
Woman	57 (50.0)	24 (46.2)	(ref)	
Man	56 (49.1)	27 (51.9)	1.15 (0.59–2.22)	0.83 (0.40–1.70)
Not specified	1 (0.9)	1 (1.9)	NA	
Missing	8	1	NA	
Medical specialty, trainees included				
Surgery	48 (42.1)	31 (59.6)	(ref)	
Oncology	66 (57.9)	21 (40.4)	0.49 (0.25–0.96)[+]	0.75 (0.33–1.71)
Missing	8	1	NA	
Clinical experience				
Specialty trainee	37 (32.5)	6 (11.5)	(ref)	
Junior consultant oncologist or surgeon	17 (14.9)	7 (13.5)	2.54 (0.74–8.71)	2.32 (0.64–8.44)
Senior consultant or equivalent experience	60 (52.3)	39 (75.0)	4.01 (1.55–10.39)[+]	3.43 (1.12–10.51)[+]
Missing	8	1	NA	NA

[+]Statistically significant (p-value < 0.05). *Not included in multivariable analysis because of high correlation between age and clinical experience, based on clinical rationale and chi-squared test. NA, not applicable.

Limited clinical experience and physician age were predictive of the degree of information provided by physicians, according to the univariable analysis (Table 14). These two variables were clinically overlapping and statistically correlated

(chi-squared test, P<0.001); therefore, age was omitted from the multivariable analysis. The odds of informing the patients about sexual side effects were 3.43 times higher for senior consultants compared with specialty trainees, after adjustments for gender and medical specialty. The factors most commonly indicated as being barriers to information were information overload, the patient being old or 'too ill' and oblivion among physicians. Interest in education was high, irrespective of clinical experience (72–88%). Among physicians, 56% *vs* 48% reported that they informed more than half of males and females, respectively, before curative treatment, and 36% *vs* 28% after treatment, respectively. The differences between sexes were statistically significant (p=0.020 and p=0.024). Sexual side effects were rarely addressed in the palliative situation.

Table 15
Clinical characteristics of rectal cancer patients (cohort 2) and logistic regression for the odds of receiving information or counselling about sexual side effects before treatment.

	Question: Did you get information and counselling regarding the treatment's effect on sexual health before the start of your cancer treatment?			
Characteristics	**'No'** N (%)	**'Yes'** N (%)	**Logistic regression,** 'yes' *vs* 'no' Odds ratio (95% confidence interval)	
N, all = 253	139 (54.9)	114 (45.1)	Univariable	Multivariable
Sex				
Male	88 (63.3)	63 (55.3)	(ref)	(ref)
Female	51 (36.7)	51 (44.7)	1.40 (0.84–2.32)	1.40 (0.80–2.46)
Missing	-	-	-	
Age, years, ǂǂ median (range)	71 (33–93)	65 (37–81)	0.72 (0.63–0.83) ǂ	0.76 (0.65–0.89) ǂ
Missing	-	-	-	-
ASA				
I–II	89 (64.0)	95 (83.3)	(ref)	(ref)
III–IV	49 (35.3)	18 (15.8)	0.34 (0.19–0.64) ǂ	0.50 (0.25–1.00) (ǂ)
Missing	1 (0.7)	1 (0.9)	NA	NA
cTNM				
I	40 (28.8)	28 (24.6)	(ref)	(ref)
II	18 (13.0)	13 (11.4)	1.03 (0.44–2.44)	0.79 (0.31–2.02)
III	73 (52.5)	61(53.5)	1.19 (0.66–2.15)	0.61 (0.27–1.36)
IV	8 (5.8)	6 (5.3)	1.07 (0.33–3.43)	0.76 (0.19–3.02)
Missing	-	6 (5.3)	NA	NA
Preoperative RT				
No	76 (54.7)	52 (45.6)	(ref)	(ref)
Yes	62 (44.6)	61 (53.5)	1.44 (0.87–2.37)	1.92 (0.94–3.92)
Missing	1 (0.7)	1 (0.9)	NA	NA
Type of surgery				
Anterior resection	88 (63.3)	84 (73.7)	(ref)	(ref)

For every 5-year increase in age, the odds of getting information about sexual side effects decreased by 24% (Table 15). Among patients with poor physical status (ASA score III–IV), the odds of being informed were half the odds for patients with ASA score I–II after adjustment for sex, disease stage, preoperative (C)RT and type of surgery.

7 DISCUSSION

Sexual function

The main finding in study II was that RT was associated with sexual function. This is in line with previous findings identifying RT as a risk factor for impaired function and dysfunction (213, 263). The randomised TME trial demonstrated decreased general female sexual dysfunction (SD) and activity, vaginal dryness and dyspareunia after treatment; however, only SD was associated with RT (121). General function and activity improved between one- and two-years follow-up in the TME study, unlike the continued decline seen here between one and two years. However, the impairments still present after two years in the TME study were permanent, and the authors concluded that preoperative RT added toxicity compared with surgery alone (122, 216). Study II demonstrated that also local symptoms were associated with RT, in agreement with the results in two Scandinavian, population-based studies (117, 229).

In Study II, the proportion with FSD was high already at baseline (66% of participants planned for RT and 96% in the surgery alone group), and increased in the RT+ group to one- and two-year follow-up. However, the standard cut-off for FSD used here, derives from a younger, predominantly premenopausal female cohort (236), making use problematic in an unselected cohort of females with RC. A comparison with similar groups could be appropriate and more informative. The figures on FSD are higher in our cohort than those reported in RC (52%–74%) in the aforementioned review, possibly because of lower participant age therein (213). Nonetheless, a substantial increase in FSD after RC-treatment was recently reported in younger females with RC, and is in line with the results here (263). Low baseline FSFI scores were expected, given the high median age (18).

In the current cohort, RT was not associated with sexual satisfaction, although with sexual desire, arousal, lubrication, orgasm, and pain. This discrepancy should be interpreted with caution, given a lower response rate in the satisfaction domain, partly explained by the prerequisite of having a partner to correctly answer those items. Nevertheless, the lack of association between RT and satisfaction could reflect that sexual dysfunction may not necessarily cause distress or dissatisfaction in ageing females, in line with findings from a review investigating the impact of ageing on sexual function (264). The authors concluded that sexually related distress remains stable or even fades with age, despite decreased sexual function. The main reason seemed to be a decline in worries about sexual performance and attractiveness and, to a lesser extent, a decrease in the importance participants attributed to sexual life. This was further supported in an English population-based longitudinal study exploring changes in sexuality with age (265), and by the Scandinavian study referred above, reporting no increased sexually related distress despite decreased function in females, unlike males (229).

There are several plausible reasons for disparities between studies exploring sexual function in females. Apart from differences in study design and questionnaires used, these studies often face a reluctance – particularly among females – to participate, resulting in low response rates. Different exclusion criteria linked to age may contribute to the disparities since increasing age correlates with lower sexual function and activity (236, 264, 266, 267).

Information about sexual side effects

In Study V, approximately half of physicians reported informing about sexual side effects before treatment, more often male than female patients – in line with the literature showing inequality in favour of males (230-232, 268, 269). In contrast, no such difference was seen in the patient cohort. About half of patients who did not get information before treatment experienced unmet informational needs, supported by existing data (228, 270). In agreement with earlier findings, patient-related barriers to information reported by physicians in Study V, were – among others - advanced age and poor physical status (230-232). Ageing is associated with decreased sexual interest and function (116, 262, 264, 265), plausibly explaining the attitudes seen among physicians. Complications of cancer and treatment increase the risk of sexual dysfunction, as already described. However, and importantly, elderly and chronically ill patients may consider sexuality important to QoL even though sexual activity and function are low at a group level (199, 233, 234, 271). Stereotypical views on sexuality in elderly and ill patients exist among healthcare professionals (234) and appear to be present among colorectal surgeons and oncologists, according to Study V and previous studies in corresponding populations (230-232).

Fertility

To assess fertility, AMH is a recognised measure of the ovarian reserve in cancer survivors, although not previously well studied in RC patients after RT (177, 186, 272). In Study II, AMH was detectable in six RT-exposed premenopausal participants at baseline, of whom five had undetectable values at follow-up and one was missing. The decreased value may reflect follicle depletion, which was expected, and supposedly caused by RT since the human oocyte has high radiosensitivity (179) and the delivered RT doses were high. In a previous study among colon cancer patients, adjuvant chemotherapy with FOLFOX caused a transient decrease in AMH and amenorrhea with complete recovery (178). In contrast, another study in CRC patients showed that only 4% of colon cancer patients had long-term amenorrhea from adjuvant chemotherapy, while the vast majority (94%) of the RC patients had amenorrhea with onset during RT (180). Therefore, adjuvant chemotherapy was not assumed to importantly contribute to iatrogenic infertility in Study II.

Psychological well-being and quality of life

In Studies II and III, psychological well-being was predictive of sexual function. However, psychological well-being at a group level remained unchanged, in line with a tendency for cancer survivors to rate their QoL as high (252, 273-276). The discrepancy between functional outcomes and QoL scores among cancer survivors has been described as a 'response shift' (277), representing a change in patients' internalised standards for rating well-being and QoL, resulting from adaption and coping strategies (278). This phenomenon complicates interpretation of longitudinal measures in QoL and comparisons with other groups (278). The participants' comments on the PGWBI (not shown here) indicate significant individual variations in the impact of disease and treatment on psychological well-being.

Sexual function assessment

The choice of the FSFI was based on its widespread and recommended use, including in cancer populations in general and in CRC, and its psychometric properties (236, 239-241, 279). Nevertheless, there are several limitations. Most importantly, there is the difficulty of assessing sexuality in patients with low or no sexual activity (240), which is common both before and after RC diagnosis. In some studies, including Study III, this is managed by excluding sexually inactive patients. Being 'sexually inactive', based on FSFI answers, may be due to high sexual dysfunction or a lack of opportunity for sexual activity (240). Sexual desire, sexual fantasies and psychological functionality may still be present and essential for QoL (280), being parts of the female sexual response cycle (199, 210, 211). In this thesis, the definition used for being 'sufficiently sexually active' for analysis of FSFI-score was wider than suggested by Baser et al., referred in *Background* (240). Despite this definition, the proportion of sexually active women at baseline was similar to previous findings (108). A total FSFI score was calculated for all complete responders, and this inclusive approach was motivated by the longitudinal design, in which each participant was its own control. Nevertheless, differences between groups may be overestimated since the baseline median FSFI score in the surgery-alone group was very low, with little room for further decrease. Calculations were repeated in sexually active females to explore this further. The association between RT and sexual function persisted, and baseline values were substantially higher in both treatment groups.

RT and androgens

Study I explored the association between RT and androgen levels. The regression analysis demonstrated an association between RT and a decline in total and free testosterone. There was no association with androstenedione or DHEAS. However, all four androgens decreased from baseline to post-treatment in the RT-exposed group, while only DHEAS decreased among the unexposed. Androgens are not primarily affected by the menopausal transition, but decline gradually with age, as previously described (167, 172, 281); thus, no drastic changes were expected during the one-year follow-up in the RT-unexposed group.

Among the androgens, DHEAS is the most age-dependent, which could explain the decrease present in DHEAS among the RT-unexposed females (282).

The endocrine function of the menopausal ovary has been debated (175). There is limited knowledge about the function of the ovarian stroma and its radiosensitivity (188, 189, 192, 283). Studies indicate a 50% decline of androgens after oophorectomy, but data are conflicting regarding the extent of decline and on how the different androgens are affected (172, 175, 191, 200, 284). The results in Study I agree with a small but statistically significant decrease in total and free T and A-4 observed in cervical cancer patients (mean age 53 years) after irradiation (191). Other studies reported a decrease in T in post- but not premenopausal cervical cancer patients after treatment (188, 189). However, these studies were conducted before laboratory methods improved substantially. The results in Study I support the idea of the menopausal ovary being an androgen-producing organ, and indicate that the androgen-producing stroma cells were damaged by the delivered radiation doses. Nevertheless, the study was not designed to answer these questions.

Androgens and sexual function

Conclusions from existing data on androgen impact on female sexual health differ. The most robust evidence in favour of an association comes from interventional studies and indicates a positive effect of T treatment on sexual function, primarily desire (196, 199, 285). Study I supports a relationship between endogenous T, free T and A-4 and sexual desire in non-oophorectomized females. In contrast, the analysis in only sexually active women in Study III, adjusted for treatment and patients variables, did not confirm that observation. In Study I, an increase in endogenous DHEAS was associated with low desire, in disagreement with earlier findings, demonstrating that low DHEAS was associated with low sexual responsiveness and, in participants younger than 45 years, low sexual desire and arousal (197). A community-based North American study demonstrated an association between high T and DHEAS and desire (202). In the same study, an association was present for high T with arousal and frequency of masturbation. Among the sexually active females in Study III, a high total endogenous T and A-4 were positively associated with FSFI total score and several FSFI domains, comprising the sexual arousal response. These results are similar to the findings in a large cross-sectional Australian study, including only premenopausal females, in which endogenous androgens had a weak, but statistically significant association with sexual function (286).

Androgen treatment in females

In 2016, the Fourth International Consultation of Sexual Medicine concluded that transdermal T in selected females with hypoactive desire disorder had sufficient efficacy and that short-term, but not long-term, safety data were available (203). This was based on data from interventional and observational studies (196, 197, 202). Another guideline from 2021 (the International Society of Women's Sexual Health), supported T use in this patient group (287). Local administration of T and DHEAS has been suggested as an option for

vulvovaginal atrophy (203). The vagina has been described as an androgen target organ (288). However, a reduced expression of androgen receptors after pelvic irradiation was observed in a histological study of vaginal tissue (289). The treatment effect from androgens could therefore be compromised in irradiated patients.

Despite data suggesting that androgens play a role in female sexuality, several aspects remain to be investigated further: For example, there is no cut-off of serum androgen levels defining insufficiency, and indication for treatment has to be based on other criteria. Knowledge gaps remain concerning the variation in androgen receptor expression and sensitivity in females and regarding the differences in the biological effects of physiological and supra-physiological (therapeutic) androgen levels (290, 291).

Radiotherapy and bone health

In Study IV, RT was associated with increased levels of the bone formation marker PINP one year after surgery, following a non-significant initial decrease. According to the crude within group analysis, BALP followed the same pattern among the RT-exposed patients. The observed trend of an initial decrease could represent an early inhibition of osteoblasts and bone formation, as reported from murine models and in line with post-radiation bone loss seen in humans (161, 292). In gynaecological cancer patients, bone density and BTMs were followed for two years after RT, and indicated a progressive damage or impaired recovery capacity (292). Bone density decreased and, in agreement with the findings in Study IV, the formation marker BALP increased from baseline to one-year post-RT. Such increase is also reported following traumatic fractures, differing in that the increase occurs early after the trauma and remains after one year (293, 294). In irradiated tissues, however, an early inhibition of bone formation and stimulation of resorption have been demonstrated (147, 292). In Study IV, no conclusion about early changes could be drawn due to few measurement points. The increased formation markers after one year could reflect an ongoing recovery phase from the radiation-induced bone damage that occurred during the first year after treatment. The findings in Study IV are neither strongly supported nor contradicted by the wide timespans reported for development of, and recovery from, RT-induced bone damage (139, 295).

The high incidence of bone damage from irradiation in the group evaluated with MRI was in agreement with two prospective studies in rectal and gynaecological cancer, respectively, also using MRI as diagnostic tool (123, 296). However, there is a wide range in incidence of PIFs after pelvic irradiation, plausibly due to methodological differences, and radiation technique, dose, and fractionation. A retrospective Danish study explored the impact of different irradiation modalities by retrospectively optimising pelvic cancer treatment-planning. The authors concluded that the use of VMAT or proton therapy could spare the sacroiliacal joints - where PIFs were most common – from high doses (297). In Study IV, the vast majority of participants had RT with box technique, and proton treatment was not yet an option.

Bowel function

Previous studies (121, 216) have demonstrated that the presence of stoma negatively impacts sexual life, although the results are contradictory (280). Thyo et al. (118) reported an association between stoma dysfunction and sexual inactivity. In Study I–IV, patients with and without stoma had low sexual function scores, with no significant difference between groups at two-year follow-up. Difficulties in demonstrating the impact of a stoma on sexual function occur partly because patients in the comparison groups frequently have LARS (125, 126, 298), which may impact sexual function (112). Another aspect confounding the interpretation is that patients undergoing surgery with APR and permanent stoma also have preoperative RT more often than patients undergoing AR. In Study I–IV, participants in the irradiated participants reported more often than participants who had surgery alone that the bowel problems had 'quite a bit' or 'a lot' of impact on sexual relationships. Thyo et al. concluded that bowel and stoma dysfunctions affected sexuality negatively, but differently (118). Bowel problems led to sexual dysfunction but not inactivity, and patients with a stoma were bothered by sexual inactivity and their physical appearance.

The utility of the bowel function questionnaire was limited as baseline data were unavailable. Moreover, the use of a scoring system other than LARS, decreased comparability with other studies.

Clinical relevance

Studies I–III

There is no established minimal clinically important difference (MCID) (299) for the FSFI, unlike the frequently used International Index of Erectile Function scale for males where the MCID depends on the severity of the baseline function (300). The observed decline in the RT-exposed participants FSFI from median value 18.5 at baseline to 10.8 two years postoperatively is assumed to be clinically meaningful.

The association between androgens and sexual function was estimated in Study I (sexual desire) as a secondary outcome and more in-depth in Study III (Global sexual function and domain scores. The reported changes in sexual function were based on one unit's change in serum androgen levels. The androgen levels were within normal ranges before and after treatment (301). Given the small reported changes in androgen levels over time, one unit's change is unlikely to occur physiologically. However, it may be relevant in the context of treatment, but uncertainty in the interpretation remains.

Study IV

The BTMs CTX-I and PINP have proven useful in osteoporosis research for fracture prediction, as a complement to established measures (157). In RC, recommendations on fracture prediction are lacking, and from Study IV of this thesis, no conclusion could be drawn regarding associations between baseline levels of bone biomarkers and bone damage during follow-up. At present, the results of this exploratory assessment of bone biomarkers have no obvious clinical impact.

Strengths and limitations

The longitudinal design in Studies I–IV has the advantage of decreasing the covariance since every subject also is its control. It enables assessments of changes over time in the measured outcomes (sexual function, androgens, and bone biomarkers) and introduces temporality between exposure and outcome variables. However, observational and longitudinal studies have limitations in terms of insufficient control over potential confounders, strongly limiting the possibility of statistical inference of the studied associations. Loss to follow-up is a common problem in longitudinal studies, decreasing the validity of results. The GEE approach applied for longitudinal statistics has the advantage of using all collected data despite missing data in a subject at some point. The model is insensitive to unbalanced data and incorrectly specified correlation matrices. These properties, and the use of robust standard errors, increase the validity of the output.

Further strengths in Studies I–IV were the choice of highly sensitive and robust tests for hormones and bone biomarkers and the multi-step dynamic method of calculating free testosterone.

Selection bias: Use of a low number of exclusion criteria increased external validity. Nevertheless, the study cohort may not be representative of the total population of females with RC, as one of the participating hospitals was a referral centre for locally advanced RC with a high proportion of participants undergoing extensive treatment, which may affect sexual function. Only Swedish-speaking patients were included, and the extent to which this may compromise the generalisability of the results remains unclear. Not all eligible females were invited to participate in the study (investigator selection), and some declined (self-selection). A selection of younger and less comorbid patients was observed in an interim analysis comparing eligible included and not included females (250). Females with poor sexual function at baseline may have chosen not to participate, introducing a selection bias towards higher FSFI scores.

In Study V, physicians interested in side effects and communication may have been overrepresented, leading to an overestimation of the provided patient information. It is unclear whether respondents in Cohort 2 represented patients with more or less unmet informational needs in the patient cohort than non-respondents.

Recall bias: The interpretation of baseline PROMs may be compromised by the impact of tumour symptoms and the psychological effects of a recently diagnosed malignant disease. Patients were therefore asked to answer based on the situation before diagnosis (if asymptomatic) or the first disease symptoms. However, this carries a risk of recall bias. The possible problem in interpretating longitudinal PROMs due to a 'response shift' has already been discussed.

Misclassification and information bias: The FSFI was developed for sexually active females in heterosexual relationships. The use in other groups may introduce misclassifications in the FSFI scores. A sensitivity analysis including only sexually active females in Study II did not significantly change the results. The possible recall bias in PROMs discussed above is assumed to be equal in both treatment groups; thus, a non-differential misclassification may be present. Efforts were made to minimise information bias in laboratory analyses. Blood samples were drawn after overnight fasting, stored at -20 °C and analysed using the same batch. Markers of bone metabolism were analysed after several years of storage, but this is not expected to affect the results as these markers are stable. In Study V, there may be a risk of overestimating information given among physicians due to a wish to perform well, and according to previous data, patients tend to underestimate the extent of information given.

Unknown or residual confounding: There may be confounding factors not included in the statistical analyses because they were either unknown, not possible to control for or only partially taken into account by an overarching variable in the statistical model. For example, co-morbidity – potentially affecting both outcome variables and the decision on preoperative RT (exposure) – was assumed to be covered by ASA score, and permanent stoma by type of surgery.

8 CONCLUSIONS

Study I

- Radiotherapy was associated with a decrease in androgens with predominantly ovarian origin.
- All four androgens were associated with sexual desire.
- The results need to be confirmed in more extensive studies and may be of interest to future interventional studies.

Study II

- Preoperative RT was associated with decreased overall sexual function and sexual arousal, lubrication, orgasm, and dyspareunia. The results support previous data.
- Undetectable AMH after RT indicated iatrogenic infertility. The results stress the importance of discussing fertility-preserving measures before treatment.

Study III

- Testosterone and A-4 were associated with overall sexual function in sexually active females. A-4, T and free T were associated with lubrication; T and A-4 with orgasm; and A-4 with arousal and dyspareunia.
- Androgens may have a role in sexual function in females with RC.
- This should be further explored, and may be of interest for interventional studies.

Study IV

- RT was associated with an increase in the bone formation marker PINP.
- RT-induced bone damage was present on MRI in 16 of 38 participants, the majority within one year from treatment. The results are in line with previous data.
- No conclusions could be drawn regarding association between RT-induced bone damage and change in bone biomarkers.
- Bone biomarkers and their potential role in RC remains to be further studied.

Study V

- Among CRC physicians, about half reported that they informed more than half of their patients, males more than females, about sexual side effects, before treatment.
- Clinical experience was predictive of providing information.
- Less than half of the RC patients reported receiving information before treatment.
- Increasing age and morbidity in patients were predictive of *not* being informed.
- Several barriers to information were identified, and the results indicate room for educational efforts among physicians.

9 FUTURE PERSPECTIVES

This thesis aimed to explore the long-term side effects of RC treatment and, more specifically, the impact on these of adding RT to surgery. It highlights the importance of continued research and measures to prevent and treat sequelae and to actively address the risk of long-term morbidity with the patients.

Future studies on preventive measures to avoid treatment side effects are of interest. An ongoing randomised trial is currently exploring the potential protective effect of PDE5 inhibitors on sexual function in males and females. Bone health could be interesting to study similarly, given that reduced vascular supply appears to be an important pathway in developing insufficiency fractures. The ongoing watch-and-wait programmes constitute a valuable platform for studying RT-specific side effects. Along with the frequent MRI evaluations being part of the follow-up protocols, bone biomarkers, sex hormones, and functional measures could be explored in more detail. The lack of a comparison group is a limitation. However, the randomised STAR-TREC trial may give a unique possibility to understand the contribution of the different treatment modalities (TME surgery, CRT or SCRT) in the development of long-term side effects.

The side effects of pelvic cancer treatment may be challenging to address for patients and their doctors, as demonstrated in this thesis. There is a need to clarify what topics should be addressed, by whom, and what the information should include as a minimum. When it comes to sexual side effects, physicians and contact nurses can be expected to screen for problems and refer to accurate expertise when appropriate. Most problems will remain undetected if professionals do not ask about the topic. There are easily implemented communication strategies, and short screening tools could facilitate communication. Education among surgeons and oncologists seems warranted to improve topic-specific knowledge and communication, preferably early during the speciality training programmes and repeatedly during the career. The pelvic cancer rehabilitation centres constitute a knowledge resource to use in educational programmes for physicians, nurses, and other health care professionals.

Possible strategies to prevent or reduce radiation fibrosis and its consequences are being studied, and could be helpful in reducing side effects in the future. Moreover, the discussed side effects may become less severe if normal tissue-sparing RT techniques are implemented to a higher degree. As the development of personalised cancer treatment continues, the role of (C)RT and surgery may change in specific groups of patients, possibly altering the future panorama of side effects for the better.

10 ACKNOWLEDGEMENTS

I would like to express my gratitude to all who have supported me in different ways throughout the work with this doctoral thesis.

I especially would like to thank;

Patients participating in the studies, without you there would be no studies – thank you!

Patients and families I meet in my daily practice, for being the source of motivation to engage in research.

Colleagues participating in Study V, for taking the time and effort to complete the questionnaire despite busy working days.

Josefin Segelman, main supervisor and former co-supervisor, for your never-ending patience and good mood, immediate responses to emails and messages, and for being motivating and encouraging throughout ups and downs. Thank you - and your family - for all the time you have spent on me.

Anna Martling, co-supervisor and former main supervisor, for being welcoming and including me in your research group; for making this thesis possible, and for your impressive work to improve colorectal cancer management.

Christian Buchli, co-supervisor, for accepting my endless need to discuss statistics. Your skills in minimalistic writing are impressive – I have a lot to learn from you!

Angelique Flöter Rådestad, co-supervisor, for sharing your indispensable expertise on hormones and lots of good advice throughout these years.

Maria Gustafsson Liljefors, my research mentor, for being wise and stable, for your laughs, and for your support when most needed.

Matteo Bottai, co-author in Study II, for contributing with biostatistical expertise in the cohort study and for teaching statistics in the most inspiring way.

Maria Sääf and Per Magnusson, co-authors in Study IV, for indispensable expertise in bone health, osteoporosis, and bone biomarkers. Thank you for inspiring collaboration.

Annika Sjövall, co-author in Study V, for generous contribution to the study, for your efficiency, positive attitude, and the work you do for pelvic cancer patients.

Madelene Ahlberg, research nurse, for your kind and professional help with all concerns regarding study I-IV.

Christina Edberg, administrator of the research group, for always being friendly, professional, helpful, and very efficient.

Ida Hed Myrberg, for revision of the statistics in Study V.

Carina Fogelberg, Jens Jensen, and Carl-Eric Leijonmarck, Capio S:t Göran's Hospital, Research Unit, for organising and hosting the public defence of the doctoral thesis, providing me with workspace, and for supporting my doctoral studies.

Mattias Hedman and colleagues, administrators, and technical support, at the Dept of Radiotherapy, Karolinska University Hospital, for being extremely helpful and friendly.

Gustav Silander, Kalle Landerholm, and all directors of study of oncology trainees, for your kind help in sending out the questionnaires in Study V.

All members of the CRC research group at MMK, KI, and special thanks to Caroline Nordenvall, for constructive and open-minded discussions during the research seminars.

Colleagues, Dpt of surgery, Capio S:t Göran's Hospital, for a good collaboration, and special thanks to my colleagues at the Division of Oncology and to Erika Isaksson Friman, for enabling combining clinical work with research and for inspiring and inclusive leadership. Colleagues at the CRC unit, Per Byström, Caroline Staff, Emma Ekefjärd, Cecilia Radkiewicz, Mona Vinblad von Walter, Sofie Rosén, and Nina Argelander, for being such a great team with high ambitions combined with a lot of smiles and laughs! Thank you all for covering up for me during these years.

Colleagues in the gastrointestinal oncology community of Stockholm, for good collaboration. Special thanks to Jan-Erik Frödin, for creating a constructive collaboration between the hospitals and always being supportive. Former colleagues at Södersjukhuset, for teaching me oncology, for all the fun, and for supporting my registration as a PhD-student.

Fredrik Baecklund, colleague and friend, for being such a good listener, always responding with well-grounded advises on research, and for everything beyond research.

My friends, for being there for me through the doctoral studies. I hope to spend much more time with you all soon!

My parents Jan and Mona Svanström, for all your loving support, and for your interest in all I do; to Björn and Kiki for being my brother and sister who make me smile, and to my aunt Mayan, for caring so much for all the family.

My extended family, for your supporting and encouraging words and actions. Speciellt tack till Clara, Ville och Victor för alla fina stunder vi har ihop och för att ni har haft tålamod med mitt jobb!

Adam, Johannes, och Linnéa, för att ni är underbara!

Last and foremost – Gustav, thanks for all your care, patience, and outstanding energy. Nothing is impossible by your side. Infinite thanks!

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12 APPENDIX

12.1 APPENDIX 1

Frågeformulär angående kvinnors sexuella funktion

Female sexual function index – FSFI © (validity of Swedish version (Ryding 2014) (302).
The question about partner is added.

Instruktioner: Dessa frågor handlar om dina sexuella känslor och reaktioner under de senaste fyra veckorna. Var vänlig besvara följande frågor så ärligt och tydligt som möjligt. Dina svar kommer att hållas helt konfidentiella. Vid besvarandet av frågorna gäller följande definitioner:

Sexuell aktivitet kan omfatta smekningar, förspel, onani eller vaginalt samlag.
Samlag definieras som penetrering (intrång i) slidan med penis.
Sexuell stimulering omfattar situationer såsom förspel med en partner, onani eller sexuell fantasi.

Kryssa **endast** en ruta per fråga

Har du en partner?
- □ Ja
- □ Nej

Sexuell lust eller **sexuellt intresse** är en känsla som omfattar lusten av att ha en sexuell upplevelse, känslan av att vara mottaglig för en partners sexuella initiativtagande, samt tankar och fantasier om att ha samlag.

1. Under de senaste fyra veckorna, hur **ofta** har du känt sexuell lust eller sexuellt intresse?
- □ Nästan alltid eller alltid
- □ Större delen av tiden (mer än halva tiden)
- □ Delar av tiden (ungefär halva tiden)
- □ Några gånger (mindre än halva tiden)
- □ Nästan aldrig eller aldrig

2. Under de senaste fyra veckorna, hur skulle du bedöma din **nivå** (grad) av sexuell lust eller sexuellt intresse?
- □ Mycket hög
- □ Hög
- □ Måttlig
- □ Låg
- □ Mycket låg eller ingen alls

Sexuell upphetsning är en känsla som innebär både fysiska och mentala aspekter. Det kan innebära känslor av värme eller pirrande i könsorganen, fuktighet eller muskelsammandragningar.

3. Under de senaste fyra veckorna, hur **ofta** har du känt dig sexuellt upphetsad (”kåt”) vid sexuell aktivitet eller samlag?
- □ Ingen sexuell aktivitet
- □ Nästan alltid eller alltid
- □ Större delen av tiden (mer än hälften av gångerna)
- □ Delar av tiden (ungefär hälften av gångerna)
- □ Några gånger (mindre än hälften av gångerna)
- □ Nästan aldrig eller aldrig

4. Under de senaste fyra veckorna, hur skulle du bedöma din **nivå** (grad) av sexuell upphetsning vid sexuell aktivitet eller samlag?
- □ Ingen sexuell aktivitet
- □ Mycket hög
- □ Hög
- □ Måttlig
- □ Låg
- □ Mycket låg eller ingen alls

5. Under de senaste fyra veckorna, hur **säker** var du på att bli sexuellt upphetsad vid sexuell aktivitet eller samlag?

- □ Ingen sexuell aktivitet
- □ Väldigt säker
- □ Mycket säker
- □ Måttligt säker
- □ Ganska osäker
- □ Mycket osäker eller fullständigt osäker

6. Under de senaste fyra veckorna, hur **ofta** har du varit tillfredsställd med din känsla av upphetsning vid sexuell aktivitet eller samlag?

- □ Ingen sexuell aktivitet
- □ Nästan alltid eller alltid
- □ Större delen av tiden (mer än hälften av gångerna)
- □ Delar av tiden (ungefär hälften av gångerna)
- □ Några gånger (mindre än hälften av gångerna)
- □ Nästan aldrig eller aldrig

7. Under de senaste fyra veckorna, hur **ofta** har du blivit fuktig (”våt”) vid sexuell aktivitet eller samlag?

- □ Ingen sexuell aktivitet
- □ Nästan alltid eller alltid
- □ Större delen av tiden (mer än hälften av gångerna)
- □ Delar av tiden (ungefär hälften av gångerna)
- □ Några gånger (mindre än hälften av gångerna)
- □ Nästan aldrig eller aldrig

8. Under de senaste fyra veckorna, hur **svårt** har det varit att bli fuktig (”våt”) vid sexuell aktivitet eller samlag?

- □ Ingen sexuell aktivitet
- □ Extremt svårt eller omöjligt
- □ Mycket svårt
- □ Svårt
- □ Lite svårt
- □ Inte svårt

9. Under de senaste fyra veckorna, hur ofta har du **bibehållit** din fuktighet till dess att sexuell aktivitet eller samlag har fullbordats?

- □ Ingen sexuell aktivitet
- □ Nästan alltid eller alltid
- □ Större delen av tiden (mer än hälften av gångerna)
- □ Delar av tiden (ungefär hälften av gångerna)
- □ Några gånger (mindre än hälften av gångerna)
- □ Nästan aldrig eller aldrig

10. Under de senaste fyra veckorna, hur **svårt** har det varit att bibehålla din fuktighet till dess att sexuell aktivitet eller samlag har fullbordats?

- □ Ingen sexuell aktivitet
- □ Extremt svårt eller omöjligt
- □ Mycket svårt
- □ Svårt
- □ Lite svårt
- □ Inte svårt

11. Under se senaste fyra veckorna, hur **ofta** har du fått orgasm genom sexuell stimulans eller samlag?

- □ Ingen sexuell aktivitet
- □ Nästan alltid eller alltid
- □ Större delen av tiden (mer än hälften av gångerna)
- □ Delar av tiden (ungefär hälften av gångerna)
- □ Några gånger (mindre än hälften av gångerna)
- □ Nästan aldrig eller aldrig

12. Under de senaste fyra veckorna, hur **svårt** har det varit att få orgasm genom sexuell stimulans eller samlag?

- □ Ingen sexuell aktivitet
- □ Extremt svårt eller omöjligt
- □ Mycket svårt
- □ Svårt
- □ Lite svårt
- □ Inte svårt

13. Under de senaste fyra veckorna, hur **tillfredsställd** har du varit med din förmåga att få orgasm vid sexuell aktivitet eller samlag?

- □ Ingen sexuell aktivitet
- □ Mycket tillfredsställd
- □ Måttligt tillfredsställd
- □ Ungefär lika tillfredsställd som otillfredsställd
- □ Något otillfredsställd
- □ Mycket otillfredsställd

14. Under de senaste fyra veckorna, hur **tillfredsställd** har du varit med den känslomässiga närheten mellan dig och din partner vid sexuell aktivitet?

- □ Ingen sexuell aktivitet
- □ Mycket tillfredsställd
- □ Måttligt tillfredsställd
- □ Ungefär lika tillfredsställd som otillfredsställd
- □ Något otillfredsställd
- □ Mycket otillfredsställd

15. Under de senaste fyra veckorna, hur **tillfredsställd** har du varit med ditt sexuella förhållande med din partner?

- □ Mycket tillfredsställd
- □ Måttligt tillfredsställd
- □ Ungefär lika tillfredsställd som otillfredsställd
- □ Något otillfredsställd
- □ Mycket otillfredsställd

16. Under de senaste fyra veckorna, hur **tillfredsställd** har du varit med ditt sexliv i allmänhet?

- □ Mycket tillfredsställd
- □ Måttligt tillfredsställd
- □ Ungefär lika tillfredsställd som otillfredsställd
- □ Något otillfredsställd
- □ Mycket otillfredsställd

17. Under de senaste fyra veckorna, hur **ofta** har du upplevt smärta eller obehag **vid** vaginalt samlag?

- □ Inga försök till samlag
- □ Nästan alltid eller alltid
- □ Större delen av tiden (mer än hälften av gångerna)
- □ Delar av tiden (ungefär hälften av gångerna)
- □ Några gånger (mindre än hälften av gångerna)
- □ Nästan aldrig eller aldrig

18. Under de senaste fyra veckorna, hur **ofta** har du upplevt smärta eller obehag **efter** vaginalt samlag?

- □ Inga försök till samlag
- □ Nästan alltid eller alltid
- □ Större delen av tiden (mer än hälften av gångerna)
- □ Delar av tiden (ungefär hälften av gångerna)
- □ Några gånger (mindre än hälften av gångerna)
- □ Nästan aldrig eller aldrig

19. Under de senaste fyra veckorna, hur skulle du bedöma din **nivå** (grad) av obehag eller smärta vid eller efter vaginalt samlag?

- □ Inga försök till samlag
- □ Mycket hög
- □ Hög
- □ Måttlig
- □ Låg
- □ Mycket låg eller ingen

12.2 APPENDIX 2

Swedish version of PGWBI score (303)

Läs detta först: Denna del av undersökningen innehåller frågor om hur du mår och hur du haft det den senaste tiden. Markera med kryss (x) i rutan det alternativ som bäst passar in på dig och din situation.

1. Hur har du i allmänhet känt dig (den senaste månaden)?

   ☐ På utomordentligt gott humör
   ☐ På mycket gott humör
   ☐ För det mesta på gott humör
   ☐ Humöret har varierat
   ☐ För det mesta på dåligt humör
   ☐ På mycket dåligt humör

2. Har du besvärats av sjukdom, fysisk åkomma, smärta eller värk (den senaste månaden)?

   ☐ Hela tiden
   ☐ För det mesta
   ☐ Ganska ofta
   ☐ Ibland
   ☐ Någon gång
   ☐ Inte alls

3. Har du känt dig nedstämd (den senaste månaden)?

   ☐ Ja, till den grad att jag känt det som om livet inte är värt att leva
   ☐ Ja, till den grad att jag inte brytt mig om någonting
   ☐ Ja, mycket nedstämd nästan varje dag
   ☐ Ja, ganska nedstämd vid flera tillfällen
   ☐ Ja, lite nedstämd då och då
   ☐ Nej, inte alls nedstämd

4. Har du haft god kontroll över ditt uppträdande, dina tankar och känslor (den senaste månaden)?

   ☐ Ja, definitivt
   ☐ Ja, för det mesta
   ☐ I allmänhet
   ☐ Inte särskilt väl
   ☐ Nej och det är ganska störande
   ☐ Nej och det är mycket störande

5. Har du känt dig nervös eller orolig (den senaste månaden)?

   ☐ Extremt mycket – till den grad att jag inte kunnat sköta vardagliga sysslor
   ☐ Väldigt mycket
   ☐ En hel del
   ☐ En del – tillräckligt för att bekymra mig

☐ Lite grand
☐ Inte alls

6. Har du känt dig energisk, pigg och vital (den senaste månaden)?

☐ Full av energi – jättepigg
☐ För det mesta energisk
☐ Min energi och vitalitet har varierat
☐ Inte så värst pigg eller energisk
☐ För det mesta slö och i stort sett utan energi
☐ Ingen energi och vitalitet alls – jag har känt mig helt urlakad och färdig

7. Jag har känt mig ledsen och missmodig (den senaste månaden)

☐ Inte alls
☐ Någon gång
☐ Ibland
☐ Ganska ofta
☐ För det mesta
☐ Hela tiden

8. Har du känt dig spänd (den senaste månaden)?

☐ Extremt spänd hela tiden
☐ För det mesta mycket spänd
☐ Ganska spänd vid flera tillfällen
☐ Lite spänd då och då
☐ Inte särskilt spänd
☐ Inte alls spänd

9. Har du känt dig lycklig, tillfredsställd och nöjd med livet (den senaste månaden)?

☐ Utomordentligt lycklig – jag skulle inte kunna vara mer nöjd och tillfreds
☐ För det mesta mycket lycklig
☐ I allmänhet lycklig och tillfredsställd
☐ Ibland lycklig – ibland olycklig
☐ I allmänhet olycklig och otillfredsställd
☐ Alltid eller för det mesta mycket olycklig och otillfredsställd

10. Har du känt dig så frisk att du kunnat göra sådant som du vill eller måste göra (den senaste månaden)?

☐ Ja, definitivt
☐ Ja, för det mesta
☐ Min hälsa har begränsat mig avsevärt
☐ Jag har bara orkat ta hand om mig själv
☐ Jag har behövt en del hjälp för att klara mig
☐ Jag har behövt hjälp med i stort sett allting

11. Har du känt dig så ledsen, modfälld eller utan hopp att du funderat på om någonting över huvud taget varit meningsfullt (den senaste månaden)?

☐ Extremt mycket, till den grad att jag varit färdig att ge upp
☐ Väldigt mycket
☐ En hel del
☐ En del – nog för att bekymra mig
☐ Lite grand
☐ Inte alls

12. Jag har känt mig fräsch och utvilad när jag vaknat (den senaste månaden)

☐ Inte alls
☐ Någon gång
☐ Ibland
☐ Ganska ofta
☐ För det mesta
☐ Hela tiden

13. Har du varit bekymrad eller orolig för din hälsa (den senaste månaden)?

☐ Extremt mycket
☐ Väldigt mycket
☐ En hel del
☐ En del
☐ Lite grand
☐ Inte alls

14. Har du känt det som om du håller på att förlora förståndet eller tappa kontrollen över dina känslor, tankar och handlingar (den senaste månaden)?

☐ Inte alls
☐ Endast lite grand
☐ Lite grand, men inte så mycket att det oroat eller bekymrat mig
☐ En del och det har oroat mig lite
☐ En hel del och det har oroat mig ganska mycket
☐ Ja, i väldigt hög grad och jag är mycket oroad

15. Mitt liv har varit fyllt av saker som intresserar mig (den senaste månaden)

☐ Inte alls
☐ Någon gång
☐ Ibland
☐ Ganska ofta
☐ För det mesta
☐ Hela tiden

16. Har du känt dig aktiv och energisk eller slö och hängig (den senaste månaden)?

- ☐ Hela tiden mycket aktiv och energisk
- ☐ För det mesta aktiv och energisk – aldrig riktigt slö och hängig
- ☐ Ganska aktiv och energisk, sällan slö och hängig
- ☐ Ganska slö och hängig – sällan aktiv och energisk
- ☐ För det mesta slö och hängig – aldrig riktig aktiv och energisk
- ☐ Hela tiden mycket slö och hängig

17. Har du känt dig orolig, upprörd eller ångestfylld (den senaste månaden)?

- ☐ Extremt mycket – till den grad att jag känt mig sjuk av oro
- ☐ Väldigt mycket
- ☐ En hel del
- ☐ En del – tillräckligt för att bekymra mig
- ☐ Lite grand
- ☐ Inte alls

18. Jag har känt mig harmonisk och säker på mig själv (den senaste månaden)

- ☐ Inte alls
- ☐ Någon gång
- ☐ Ibland
- ☐ Ganska ofta
- ☐ För det mesta
- ☐ Hela tiden

19. Har du känt dig avslappnad och lugn eller stressad, spänd och uppskruvad (den senaste månaden)?

- ☐ Hela tiden avslappnad och lugn
- ☐ För det mesta avslappnad och lugn
- ☐ Oftast lugn men då och då ganska spänd
- ☐ Oftast spänd men vid enstaka tillfällen ganska avslappnad
- ☐ För det mesta stressad, spänd och uppskruvad
- ☐ Hela tiden stressad, spänd och uppskruvad

20. Jag har känt mig glad och sorglös (den senaste månaden)

- ☐ Inte alls
- ☐ Någon gång
- ☐ Ibland
- ☐ Ganska ofta
- ☐ För det mesta
- ☐ Hela tiden

21. Jag har känt mig trött och slutkörd (den senaste månaden)

☐ Inte alls
☐ Någon gång
☐ Ibland
☐ Ganska ofta
☐ För det mesta
☐ Hela tiden

22. Har du känt dig stressad, pressad eller jäktad (den senaste månaden)?

☐ Ja, på gränsen till vad jag har orkat med
☐ En hel del stress
☐ En del – mer än vanligt
☐ En del – ungefär som vanligt
☐ Lite grand
☐ Inte alls

Dina kommentarer:
……
……

12.3 APPENDIX 3

Questionnaire on bowel function (Modified Miller Score) with two additional questions regarding impact of bowel and urinary function on sexual relations.

Karolinska Institutet

Patient nr: ☐☐☐
Initialer: ☐☐☐
Besök: 3

Frågeformulär angående tarmfunktion hos kvinnor behandlade för ändtarmscancer

Syftet är att utvärdera din tarmfunktion. Kryssa för det alternativ som stämmer bäst. Frågorna gäller både dig som har och inte har stomi.

Kryssa **endast** en ruta per fråga.

1. Har du stomi
   - ☐ Ja
   - ☐ Nej

2. Har du ofrivillig gasavgång?
   - ☐ Aldrig
   - ☐ Mellan en gång/vecka och en gång/månad
   - ☐ Mellan en gång/dag och en gång/vecka
   - ☐ En eller flera gånger/dag

3. Har du läckage av **lös** avföring?
   - ☐ Aldrig
   - ☐ Mellan en gång/vecka och en gång/månad
   - ☐ Mellan en gång/dag och en gång/vecka
   - ☐ En eller flera gånger/dag

4. Har du läckage av **fast** avföring?
   - ☐ Aldrig
   - ☐ Mellan en gång/vecka och en gång/månad
   - ☐ Mellan en gång/dag och en gång/vecka
   - ☐ En eller flera gånger/dag

Följande två frågor gäller **de senaste fyra veckorna:**

5. Har din tarmfunktion och/eller stomi haft en negativ inverkan på ditt sexuella samliv?
   - ☐ Inte alls
   - ☐ Lite
   - ☐ En hel del
   - ☐ Mycket
   - ☐ Ej relevant

6. Har urinvägsbesvär haft en negativ inverkan på ditt sexuella samliv?
   - ☐ Inte alls
   - ☐ Lite
   - ☐ En hel del
   - ☐ Mycket
   - ☐ Ej relevant