Lower Gastrointestinal Research Group
Department of Molecular Medicine and Surgery
Karolinska Institutet, Stockholm, Sweden

COLORECTAL CANCER

ASPECTS OF MULTIDISCIPLINARY TREATMENT, METASTATIC DISEASE AND SEXUAL FUNCTION

Josefin Segelman

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To Jerker, Eira, Aina and Justus

Contents

Abstract

More than 6000 people in Sweden are diagnosed with colorectal cancer annually. One out of five patients already has metastases at diagnosis. However, the occurrences of metastases at specific locations, e.g. peritoneal carcinomatosis and ovarian metastases, are not well known. The development of surgical and oncological treatment strategies for primary tumours and metastatic disease has led to a need to discuss colorectal cancer patients in a multidisciplinary team (MDT). Although oncologic cure and overall survival are the main goals of treatment, quality of life and functional results are becoming increasingly important with the prolonged survival. While male sexual dysfunction after rectal cancer treatment has been well described, considerably less data have been published about the impact on women. In addition to surgical trauma, female androgen insufficiency could be a contributing factor to sexual dysfunction. Radiotherapy for rectal cancer may increase the risk of reduced ovarian androgen production, but there is scant information on this in the literature.

Papers I-III are large population-based cohort studies reporting on the effects of the development and implementation of MDT-conferences in patients with metastatic disease (Paper I) and the epidemiology of peritoneal carcinomatosis and ovarian metastases in colorectal cancer patients (Papers II–III). MDT assessment and metastasis surgery were more common in rectal cancer patients than in colon cancer patients, and the proportion increased over time. Peritoneal carcinomatosis was common, and risk factors were colon cancer, advanced tumour and nodal stage, fewer than 12 examined lymph nodes, emergency surgery, and a non-radical resection of the primary tumour. Ovarian metastases were uncommon, especially in rectal cancer patients. Paper IV assesses feasibility and internal and external validity in a prospective, observational cohort study on sexual function and androgen levels in women with rectal cancer. The methods were workable and the patients' compliance was good. Comparison of clinical data from the study cohort with that of women who were eligible for inclusion but not included revealed a selection bias. Having a partner and sexual activity was more common among women who answered all questions in the questionnaires about sexual function compared with those who did not. A power calculation based on data from the first included patients showed that a larger sample size than initially planned for was needed.

In conclusion, an increasing proportion of patients with metastatic colorectal cancer were discussed by the MDT. Predictors for and the occurrence of peritoneal carcinomatosis and ovarian metastases were defined, which may help to decide on individual treatment and follow-up regimens. The analysis of baseline data from the study on sexual function and androgen levels in women with rectal cancer indicates feasible methods but a selection bias. Inclusion of new patients in the study continues.

List of Papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I **Differences in multidisciplinary team assessment and treatment between patients with stage IV colon and rectal cancer**
J. Segelman, T. Singnomklao, H. Hellborg, A. Martling
Colorectal Disease
2009; 11: 768-774

II **Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer – a population based study**
J. Segelman, F. Granath, T. Holm, M. Machado, H. Mahteme, A. Martling
British Journal of Surgery
2012; Epub ahead of print

III **Epidemiology and prognosis of ovarian metastases in colorectal cancer**
J. Segelman, A. Flöter-Rådestad, H. Hellborg, A. Sjövall, A. Martling
British Journal of Surgery
2010; 97: 1704-1709

IV **Potential selection bias in a prospective study on sexual function and androgen levels in women with rectal cancer**
J. Segelman, A. Martling, M. Machado, T. Holm, K. Bergmark, A. Flöter Rådestad
Manuscript

Abbreviations

ASA	American Society of Anesthesiologists
CEA	Carcinoembryonic antigen
CI	Confidence interval
CME	Complete mesocolic excision
CRM	Circumferential resection margin
CRS	Cytoreductive surgery
CT	Computed tomography
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FAI	Female androgen insufficiency
FSFI	Female Sexual Function Index
HIPEC	Hyperthermic intraperitoneal chemotherapy
HR	Hazard ratio
MDT	Multidisciplinary team
MRF	Mesorectal fascia
OR	Odds ratio
PC	Peritoneal carcinomatosis
PCI	Peritoneal Carcinomatosis Index
PET	Positron-emission tomography
RT	Radiotherapy
SHBG	Sex hormone-binding globulin
SOE	Salpingo-oophorectomy
SOEB	Bilateral salpingo-oophorectomy
T	Testosterone
TME	Total mesorectal excision

INTRODUCTION

Epidemiology and Etiology

Colorectal cancer is one of the most common cancers worldwide. The highest incidence rates are found in Australia, North America and Western Europe, whilst the lowest are found in developing countries [75]. In Sweden, colorectal cancer is the third most common form of cancer in both sexes, after prostate and skin cancer in men, and after breast and skin cancer in women. In 2009, 3256 men and 2924 women were diagnosed with colorectal cancer [222]. Incidence rates have increased slightly over the past decades (*Fig. 1*) [5 6]. The incidence of cancer of the proximal colon is higher in women than in men, while men have a higher incidence of cancer in the distal colon and rectum [195].

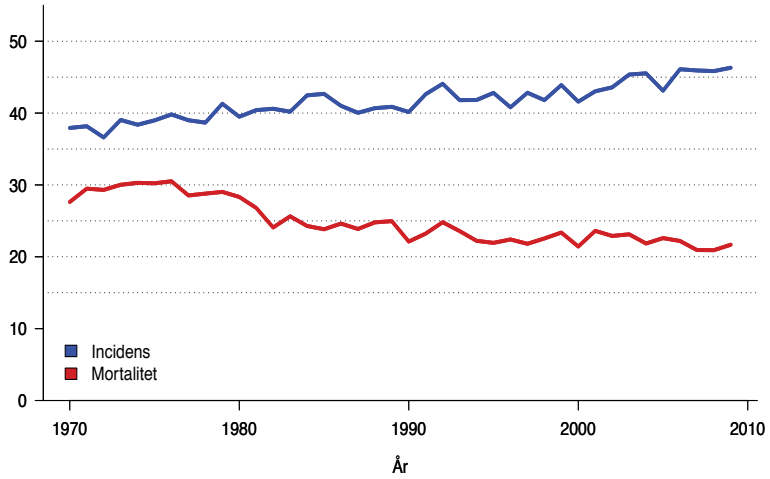


Figure 1a. *Age-standardized incidence of and mortality from colon cancer per 100.000 male inhabitants in Sweden, 1970–2009*

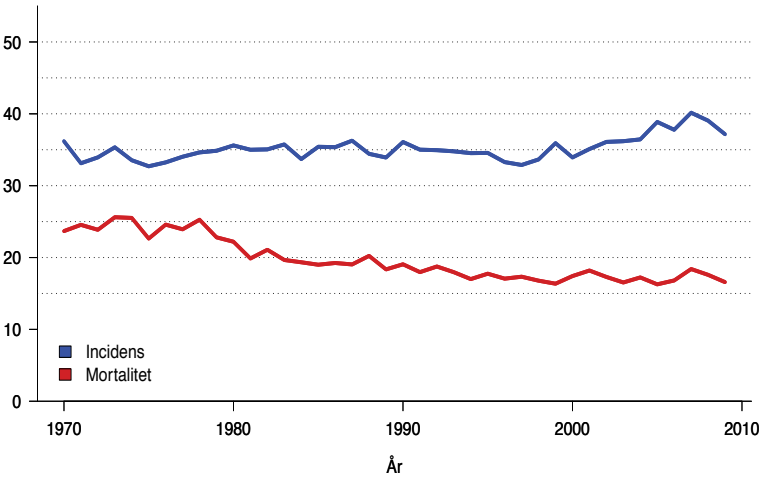


Figure 1b. *Age-standardized incidence of and mortality from colon cancer per 100.000 female inhabitants in Sweden, 1970–2009*

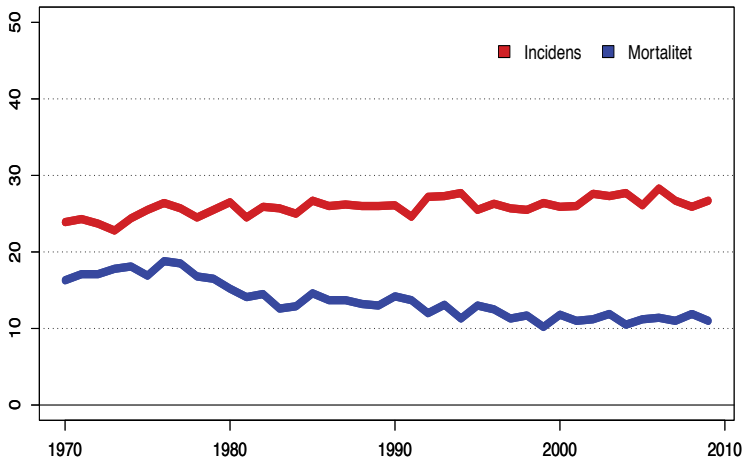


Figure 1c. *Age-standardized incidence of and mortality from rectal cancer per 100.000 male inhabitants in Sweden, 1970–2009*

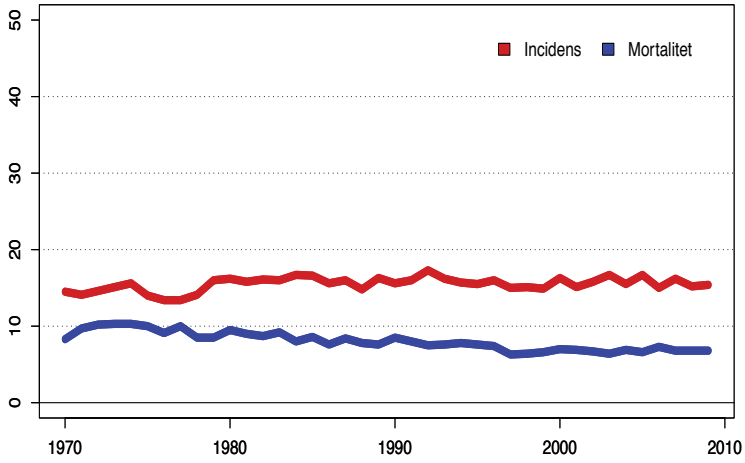


Figure 1d. *Age-standardized incidence of and mortality from rectal cancer per 100.000 female inhabitants in Sweden, 1970–2009*

Predictors for developing colorectal cancer include hereditary factors, advanced age, male sex, previous polyps or colorectal cancer, inflammatory bowel disease, obesity, and diabetes mellitus [57] [195]. Associated lifestyle and dietary factors include low physical activity, a low intake of dietary fibers and high intake of fat and red meat, smoking, and high alcohol consumption. Studies on sex hormone-related factors report a decreased risk of colorectal cancer with endogenous and exogenous estrogen exposure, as well as androgen deprivation therapy [31] [65] [85] [94]. Some of the predictors may explain the geographical variations and the differences in incidences between men and women.

Adenoma is the precursor to colorectal cancer. About 10% of adenomas progress to invasive cancers via several steps of genetic changes in a process lasting approximately 10 years [57] [267]. Kindred and twin studies estimated that approximately 30% of all colorectal cancers are an inherited form of the disease [57] [115]. The most common genetic syndromes are familial adenomatous polyposis (FAP) syndrome and hereditary non polyposis colorectal cancer (HNPCC) syndrome, together accounting for about 5% of all colorectal cancers.

About 20% of patients with colorectal cancer already have metastatic disease at diagnosis of the primary tumour [5 6 53]. The most frequently reported site for distant metastases is in the liver [8] . The reason for this is the direct venous drainage from the bowel to the portal vein system. Other sites of metastatic disease that are specifically addressed in this thesis are the peritoneum and the ovaries. Knowledge about the epidemiology and risk factors of peritoneal carcinomatosis (PC) is limited and population-based studies are lacking. Previously, synchronous and metachronous PC have been reported in 2-19% of colorectal cancer patients [117 131]. Possible predictors of developing metachronous PC described in the literature are liver metastases, tumour (T) stage, nodal (N) stage, venous and perineural invasion, synchronous limited PC diagnosed with the primary tumour, synchronous ovarian metastases, and perforated or obstructive primary tumour [71 117 264]. The mechanisms causing PC are multifactorial and include hematogenous or lymphatic spread, peritoneal dissemination from serosal involvement of the primary tumour, and implantation of free cancer cells in lymph fluid or venous blood during surgery or in the case of perforation of the primary tumour [112 233].

Similarily to PC, the occurrence of ovarian metastases in women with colorectal cancer is not well known. Previous studies from single centres report synchronous ovarian metastases in 0–9% of women with colorectal cancer and metachronous ovarian metastases in 0.9%–7% [93 101 127 209 274]. Ovarian metastases are reported to be associated with PC and to be more common in relatively young women [49 74 127 147 198 240]. The pathogenesis may be trancoelomic or lymphovascular [275].

Survival

The age-adjusted 5-year survival for colorectal cancer patients has increased substantially over time in Europe, in particular in rectal cancer patients, and it is high in Sweden [37 181]. The relative 5-year survival for patients diagnosed with colon cancer in Sweden during 2005–2009 was 65.4% for women and 60.9% for men [5]. The corresponding figures for rectal cancer were 64.1% and 60.9% [6]. The strongest prognostic factor is tumour stage [109]. In patients with localized colorectal cancer, 5-year relative survival reaches 90%, compared to 5–15% in patients with metastatic disease [37]. The only treatment achieving long-term survival in patients with metastatic disease is surgical resection of the primary tumour and the metastases. In patients with liver metastases, hepatic resection, when feasible, is associated with an improved prognosis [130]. Five-year survival after potentially curative resection of liver metastases ranges between 30% and 58% [219].

Peritoneal Carcinomatosis

Peritoneal carcinomatosis from colorectal cancer has been regarded as a terminal condition with a median survival historically reported to be around six months [48 117 208]. More recent palliative chemotherapy protocols based on the use of oxaliplatin, irinotecan, and biological agents have resulted in an improved prognosis in stage IV colorectal cancer patients, with

a median survival reaching 24 months [171] [211] [249]. Unfortunately, none of these trials provide data on survival for patients with isolated peritoneal dissemination. In contrast, an increasing number of studies have reported long-term survival in PC patients treated with cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC), in particular in those where complete cytoreduction can be achieved [70] [154] [258]. The rationale is to use the combination of cytoreductive surgery to treat macroscopic disease with perioperative intraperitoneal chemotherapy to treat microscopic disease [238] [239]. This is the only strategy that has shown curative results for PC in a randomized controlled trial and international register studies [70] [87] [258]. An update of the randomized controlled trial reported a 45% 5-year survival in patients receiving optimal cytoreduction and HIPEC followed by systemic chemotherapy [257]. In a retrospective analysis of a multicentre cohort of more than 500 patients treated with CRS and HIPEC, median and 5-year overall survival were 30.1 months and 27 %, respectively [70]. Two comparative studies of patients with isolated PC have reported a median survival of 35-63 months in patients treated with CRS and HIPEC versus 17- 24 months in patients treated with aggressive systemic chemotherapy alone [72] [79].

Ovarian Metastases

Survival in women with ovarian metastases depends on whether surgery can make the patient free from tumour or not. Tumour confined to the ovaries or the pelvic cavity, unilateral ovarian involvement, a macroscopically radical resection, normal carcinoembryonic antigen (CEA) level, chemotherapy and a good performance status are independent favourable prognostic factors [49] [80] [127] [144] . The reported median survival after resection of colorectal ovarian metastases is 31–61 months when complete resection can be achieved and 7–15 months when resection is incomplete [80] [162] [198].

Clinical Staging

Primary Tumour

Investigations for preoperative staging include radiology for colon and rectal cancer as well as digital examination and rectoscopy for rectal cancer.

Computed tomography (CT) of the abdomen can be used for staging of the primary tumour in colon cancer patients. In patients with rectal cancer, ridgid rectoscopy is used to assess the distance of the tumour from the anal verge. Pelvic magnetic resonance imaging (MRI) gives detailed information on the primary rectal cancer and regional lymph nodes. This imaging modality distinguishes the mesorectal fascia (MRF), which forms the potential circumferential resection margin (CRM) [89]. MRI is superior in evaluating the risk of a postoperative involvement of this margin (CRM+), which helps to select patients for neoadjuvant treatment and also to evaluate treatment response prior to surgery [241]. Diffusion-weighted MRI is a promising method for distinguishing between tumour and fibrosis after radiochemotherapy [107]. Recent data report improved selection of complete responders to neoadjuvant radiochemotherapy us-

ing diffusion-weighted MRI compared to standard pelvic MRI [141]. Endorectal ultrasound is sometimes indicated for assessing tumour growth within the bowel wall. It gives high resolution images within a limited field of view, and is therefore superior to MRI in assessing the mural invasion in superficial bowel layers [123]. However, the technique is not accurate in the detection of mesorectal metastatic lymph nodes [139].

Distant Metastases

Computed tomography (CT) of the abdomen and CT or x-ray of the lungs are used for the assessment of distant metastases in both colon and rectal cancer. Contrast–enhanced ultrasound or liver-specific MRI can give additional information if CT is inconclusive. Peritoneal metastases are sometimes diagnosed in preoperative radiological examinations even though early detection of PC is still a radiological challenge. According to an international consensus, contrast-enhanced multidetector CT is the procedure of choice in the evaluation of PC in patients eligible for CRS and HIPEC [270]. However, the procedure is limited by the difficulty in early nodule detection in thin patients without ascites, which may be the case in many patients with early tumour dissemination. The sensitivity of preoperative CT in detecting peritoneal implants is influenced by lesion size. Secondary CT features may be helpful in identifying the disease. These include distortion, obstruction and wall thickening of the small bowel and obstruction of extrahepatic bile ducts. Unfortunately, when patients present with these CT features as well as the presence of para-aortic lymph node metastases, the disease is usually too advanced to be salvaged by CRS and HIPEC. Positron-emission tomography (PET) with the tracer fluorodeoxyglucose plays an increasingly important role in the diagnosis, staging, and surveillance of malignant disease [26]. The combination of functional PET data and detailed anatomical information provided by CT in dual modality PET/CT further improves staging accuracy [15]. Early results with regard to aiding the selection of patients for CRS and HIPEC are promising [186] [190]. It is important, however, to know that a PET scan may not detect mucinous or low-grade malignant tumours and it can produce false positive results in cases of acute inflammation or active tissue repair, i. e., after surgery.

Ovarian metastases may be detected with CT, MRI, ultrasound or PET/CT [128]. Typically CT and MRI show unilocular or multilocular cystic masses, associated with variable degrees of solid components (*Fig. 2*) [132]. In the case of bilateral ovarian tumours, metastatic disease is likely since bilateral primary ovarian mucinous adenocarcinomas are rare.

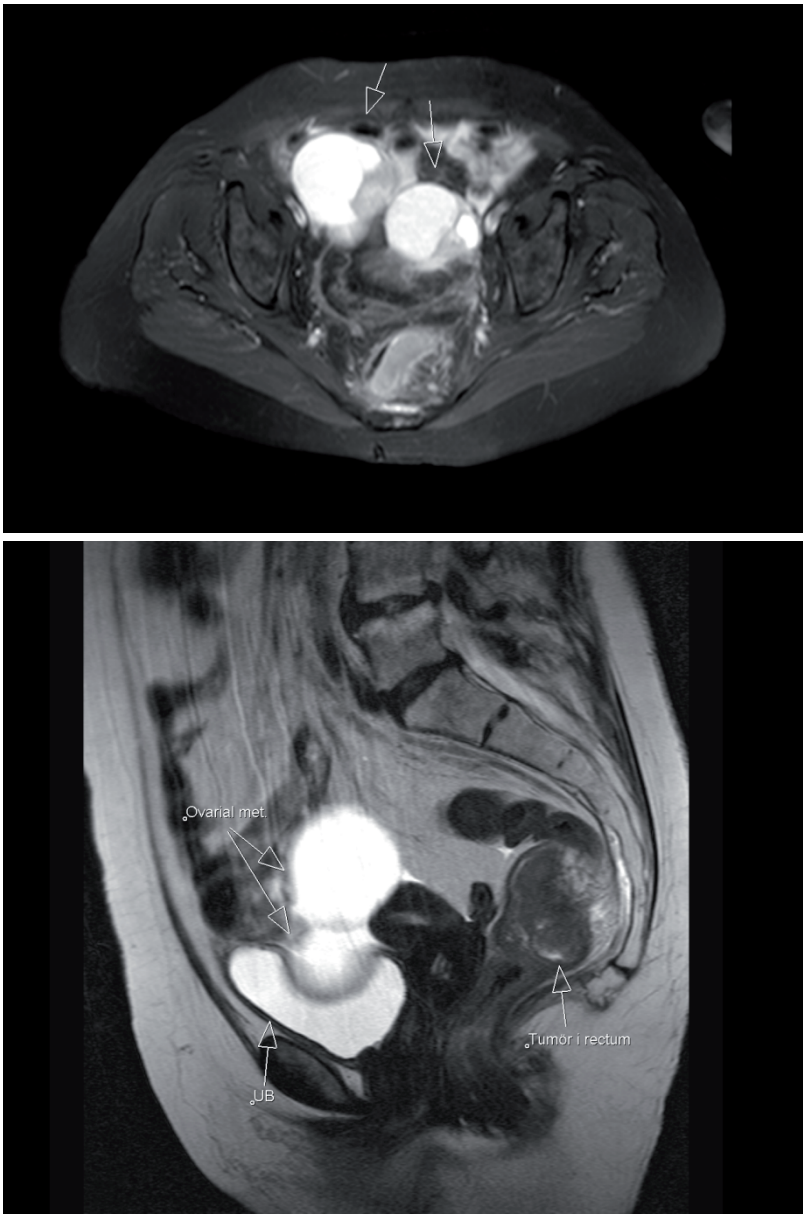


Figure 2. *MRI presentation of bilateral ovarian metastases from rectal cancer (arrows). UB: urinary bladder*

Multidisciplinary Team Conference

Treatment of colorectal cancer involves specialists from multiple disciplines. With the development of radiological staging and new treatment strategies, multidisciplinary team (MDT) conferences have become the model of care [140] [173]. The team includes surgeons, radiologists, oncologists, pathologists and specialized nurses. Each colorectal cancer patient should be discussed individually both pre- and postoperatively according to the guidelines of the National Board of Health and Welfare [224]. Tumour stage, co-morbidity, social circumstances, and the wishes of the patient are taken into account. The aims are to facilitate communication and coordination between health care professionals and, above all, improve decision–making regarding optimal treatment for the individual patient. Through regular meetings, team members

will become more aware of efficient ways of treatment planning, simplification of referral processes, and avoidance of the duplication of examinations and investigations [206]. MDT working should also provide team members with educational opportunities to learn about new treatment developments and clinical trial recruitment. An association between the introduction of colorectal cancer MDT working with a change in treatment decisions has been reported [150]. In an international study, MDT assessment influenced decisions about staging methods and neoadjuvant treatment of rectal cancer patients [17]. Furthermore, in a study on treatment decisions at a colorectal cancer MDT, the vast majority of the decisions were implemented [269]. MDT discussion of MRI and implementation of a preoperative treatment strategy has been shown to reduce positive circumferential resection margins (CRM+) in patients with rectal cancer [43]. In a review examining the relationship between multidisciplinary cancer care and patient survival, a significant positive association was reported in 12 of 21 studies, including 3 on colorectal cancer [111]. The proportion of colon and rectal cancer patients assessed by an MDT in Sweden has gradually increased. Differences between regions vary, in particular for colon cancer (*Fig. 3*) [5 6].

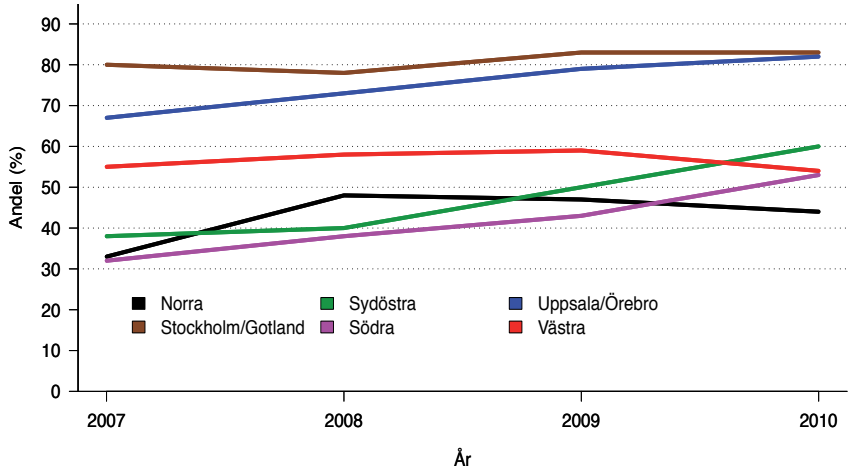


Figure 3a. *Proportion of patients assessed postoperatively by an MDT after elective surgery for colon cancer, 2007–2010, by region.*

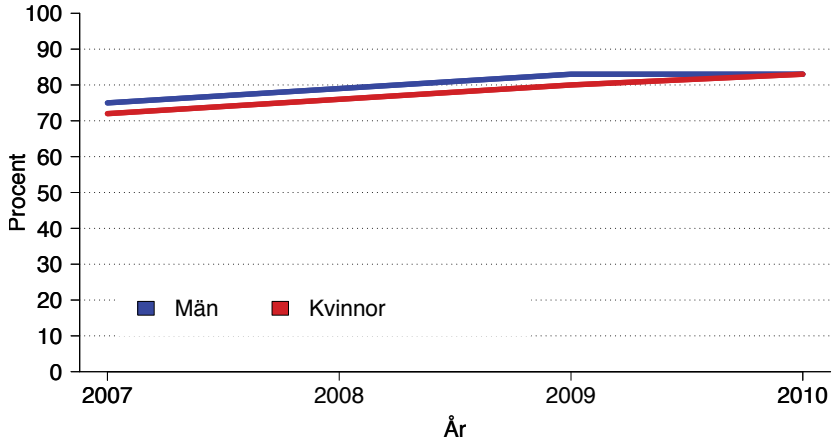


Figure 3b. *Proportion of rectal cancer patients assessed by an MDT before treatment in Sweden, 2007-2010.*

Histopathological Staging

Tumour, Node, Metastasis Staging

The most frequently used system for staging colorectal cancer is the TNM staging system, which is universal for all anatomic sites (*Table 1*) [221]. The system has been developed by the International Union against Cancer (UICC) and the American Joint Commission of Cancer (AJCC) and has the primary advantage of being a detailed, independent classification within each subcategory (T, N, M). The relationship between the earlier Dukes' classification and TNM systems is shown in *Table 2* [69].

Table 1. TNM classification 7th edition[221]

TNM classification 7th edition		
Primary tumour (T)	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
	Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
	T1	Tumour invades submucosa
	T2	Tumour invades muscularis propria
	T3	Tumour invades through the muscularis propria into the subserosa or pericolorectal fat
	T3a	Minimal invasion: < 1 mm beyond the borders of the muscularis propria
	T3b	Slight invasion: 1–5 mm beyond the borders of the muscularis propria
	T3c	Moderate invasion: >5–15 mm beyond the borders of the muscularis propria
	T3d	Extensive invasion: > 15 mm beyond the borders of the muscularis propria
	T4a	Tumour penetrates to the surface of visceral peritoneum
	T4b	Tumour directly invades or is adherent to other organs or structures
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in 1–3 regional lymph nodes
	N1a	Metastasis in one regional lymph node
	N1b	Metastasis in 2–3 regional lymph nodes
	N1c	Tumour deposit(s), i.e. satellites, in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal mestastasis
	N2	Metastasis in 4 or more regional lymph nodes
	N2a	Metastasis in 4–6 regional lymph nodes
	N2b	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Metastasis confined to one organ or site (for example liver, lung, ovary, non-regional node)
	M1b	Metastases in more than one organ/site or the peritoneum

Table 2. Systems for classification of colorectal cancers

AJCC/UICC staging system	TNM classification 7th edition	Dukes' classification
Stage 0	**Tis, N0, M0**	**-**
Stage I	**T1–T2, N0, M0**	**A** Tumour limited to bowel wall
Stage II	**T3–4, N0, M0** *Stage IIA:* T3, N0, M0 *Stage IIB:* T4A, N0, M0 *Stage IIC:* T4B, N0, M0	**B** Tumour growth outside the bowel wall
Stage III	**Any T, N1–N2, M0** *Stage IIIA:* T1–T2, N1, M0 T1, N2a, M0 *Stage IIIB:* T3–T4a,N1, M0 T2–T3, N2a, M0 T1–T2, N2b, M0 *Stage IIIC:* T4a, N2a, M0 T3–T4a, N2b, M0 T4b, N1–N2, M0	**C** Lymph node involvement
Stage IV	**Any T, Any, N M1** *Stage IVA:* Ant T, Any N, M1a *Stage IVB:* Any T, Any N, M1b	**D** Distant metastases

Residual Tumour Classification

The tumour status regarding presence or absence of residual tumour after treatment is described by the Residual (R) Tumour Classification (*Table 3*) [221]. The R classification reflects the effects of treatment, influences further treatment planning and is a strong predictor of the prognosis [109].

Table 3. Residual Tumour Classification

R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour

Resection Margins

The CRM is the minimal distance from the outermost part of the tumour or malignant tissue to the lateral margin of the resected specimen. The malignant tissue could be a discontinuous spread of the primary tumour or, tumour in veins or lymphatic tissue. For parts of the bowel that are nearly totally enclosed by the peritoneum (ceacum, transverse and sigmoid colon), the CRM constitutes the mesenteric resection margin. Involvement of the CRM has a negative impact on local and distant recurrence rates and survival [102 176 196 214]. Microscopic tumour growth in the resection margin or a minimal distance of <1 mm from the tumour to the resection margin has been considered to be CRM-positive (CRM+) in most studies. However, some studies indicate that a margin of 2 mm is a more relevant cut-off value [175].

Surgical Treatment

Colon Cancer

Surgery with resection of the colon segment containing the tumour and its regional lymph nodes is the primary treatment for colon cancer. Continuity is restored with a hand-sewn or stapled anastomosis, or a stoma is performed. Compared to traditional surgery, the more radical complete mesocolic excision (CME) is reported to be beneficial in terms of a greater lymph node yield [260]. This finding may explain the low local recurrence rates and high survival after such surgery in reported consecutive series [110]. The concept of CME is sharp dissection of the visceral fascia from the parietal one so as to result in complete mobilization of the entire mesocolon covered by an intact visceral fascia layer on both sides thereby ensuring safe exposure and tying of the supplying arteries at their origin. This concept is gaining ground in Sweden. A possible increased risk of complications has to be taken into account, however, when adopting the technique of central dissection at the roots of the vessels.

The standard surgical approach in Sweden is open surgery. In 2009, only 3% of resections for colon cancer were performed laparoscopically [5]. The laparoscopic technique has been evaluated in randomized controlled trials, which have shown that it is not inferior to open surgery regarding cancer-free survival [44 118].

Rectal Cancer

The golden standard for rectal resection is total mesorectal excision (TME), which minimizes the risk of local recurrence and avoids injury to the autonomic nerves innervating the pelvic organs [105 106 151]. The introduction of the TME technique has led to improved cancer-specific survival [160]. TME surgery includes sharp dissection under direct vision in the avascular plane surrounding the mesorectum down to the pelvic floor. The superiority of the method compared to the traditional blunt dissection has been confirmed in histopathological studies [196]. Theoretically, the hypogastric and pelvic nerves are identified and preserved. Even if nerves are preserved, however, injury may still occur as a result of retraction, devascularisation, and cautery. The inferior mesenteric artery may be divided close to the aorta and proximal to the origin of the left colic artery (high tie), with a theorectially more oncologically sound operation, as well as more accurate tumour staging [121]. Alternatively, because of concerns regarding the risk of autonomous nerve damage and possible ischemia in the proximal bowel end with a risk of anastomotic leakage, the inferior mesenteric artery may be divided distal to the origin of the left colic artery (low tie).

Anterior resection of the rectum with anastomosis is performed when an adequate distal tumour margin can be achieved with an acceptable functional result. If the tumour is located in the upper third of the rectum, a partial mesorectal excision with perpendicular transsection of the mesorectum at least 5 cm below the tumour is considered to be sufficient. The anastomosis is most frequently performed with a circular stapling device. In tumours of the middle and distal part of the rectum the resected rectum can be replaced using a side- to-end-anastomosis or J-pouch in order to mitigate the functional disorder [98 99 152].

Anastomotic leakage is a common complication with high morbidity and occurs in about 9% of Swedish patients after anterior resection for rectal cancer [6]. The occurrence of clinically significant anastomotic leakages is reduced by the use of a temporary loop-ileostomy, which is therefore recommended after anterior TME-resections [161].

Abdominoperineal resection is performed when the tumour is situated in the distal part of the rectum or when unacceptable functional results are expected with an anastomosis. For the low-lying rectal cancer, there is almost no mesorectal fat, and the risk of CRM+ or an R1/2 resection is imminent. Because of the anatomy of the pelvic floor, abdominal dissection will end up with a coned specimen with a waist at the entrance of the anal canal where the tumour is located. If the procedure is stopped from above and started earlier from below, the surgeon can follow the pelvic floor laterally, thereby creating a more cylindrical specimen and thus avoiding a positive CRM [259].

If the tumour invades adjacent organs, an extended surgical procedure is necessary [182]. Depending on tumour growth and the expected reconstruction of organs, the operating team is often multidisciplinary, comprising vascular surgeons, urological surgeons and plastic surgeons besides the colorectal surgeon. A carefully planned extended TME is mandatory to achieve an R0 resection in patients with locally advanced rectal cancer. Involved adjacent organs are resected en bloc with the rectum – if necessary including the ureters, bladder, small bowel, pelvic floor, nerves, blood vessels and sacrum. In men, the prostate and the seminal vesicles and, in women, the uterus, ovaries and vagina are removed if necessary.

In the earliest and most favourable cases of rectal cancer, e.g. malignant polyps, a local procedure using the transanal endoscopic microsurgery (TEM) technique can be appropriate. This technique can be used provided that the resection is radical (R0) and no signs of poor differentiation or vessel invasion are present.

Radiotherapy and Radiochemotherapy

Preoperative radiotherapy for rectal cancer reduces local recurrences and increases the cancer-specific survival [1 3 45 47 122 159 250] . These benefits have to be weighed against the adverse side effects. Well-known acute and long-term complications include erythema of the skin, nausea and diarrhea, cystitis, lumbosacral plexopathy, osteoradionecrosis, impaired sphincter function, urinary and sexual dysfunction, increased risk of postoperative ileus, and a doubled risk of secondary malignancies [24 142 157 193]. Optimal clinical staging is crucial to select patients who will benefit most from preoperative radiotherapy. Tumours can be classified as “good”, “bad” or “ugly” based on the MRI findings [27]. The Swedish national guidelines are based on this classification [2]. Somewhat simplified, early rectal cancer (“good”) has a low risk of recurrence and should be treated with surgery alone, for intermediately advanced tumours (“bad”) with an otherwise unacceptable risk of local recurrence, short-course radiotherapy immediately followed by surgery is recommended, and for the locally advanced cancers (“ugly”) with a high risk of non-radical resection, preoperative long-course radiochemotherapy and delayed surgery are recommended (*Fig. 4*) [90]. In patients considered to be too frail for the combined modality therapy, a possible alternative is short-course radiotherapy with renewed clinical and radiological evaluation after 6 weeks [189].

Favourable ”good” group	Intermediate ”bad” group	Advanced ”ugly” group
Mid/upper rectum T1-T3b Low rectum T1-2 N0	Mid/upper rectum T3c/d Low rectum T3 T4 with peritoneal or vaginal involvement only N1/N2	T4 with overgrowth to prostate, seminal vesicles, base of urinary bladder, pelvic side walls or floor, sacrum Positive lateral lymph nodes
MRF clear	MRF clear	MRF involvement (MRF+)
↓	↓	↓
Primary surgery	Preop 5 x 5 Gy with immediate surgery	Preop RTCT or 5 x 5 Gy with delayed surgery

RTCT: Radiochemotherapy up to 50.4 Gy in 1.8-Gy fractions with 5-fluorouracil (5-FU).

Figure 4. *Neoadjuvant treatment of rectal cancer according to clinical stage. Modified from Blomqvist/Glimelius* [27]

Target Volume and Fractionation

Today radiotherapy is administered using a four-field technique. Information from CT is used for increased precision in target volume and optimal dose planning.

The aim of short course radiotherapy (5 x 5 Gray during one week) in patients with ”bad” rectal cancers is to eradicate tumour cells in the surrounding tissues, i.e. primary mesorectal lymph nodes and secondary lymph nodes laterally, presacrally, and along the superior rectal artery. The anal canal is included in the target volume in low rectal cancers where an abdominoperineal resection is scheduled. Surgery is performed within a week after termination of the radiotherapy. The optimal fractionation and timing to surgery remains controversial. An ongoing randomized study, the Stockholm III trial, addresses these issues [188].

In patients with locally advanced ”ugly” cancers, the target volume is modified according to the extent of the tumour. A daily dose of 1.8 Gray up to a total dose of 50.4 Gray is combined with chemotherapy. The purpose of this strategy is to attain resectability by tumour regression before surgery. The chemotherapeutic agent can serve as a radiosensitizer on the primary tumour and micrometastatic disease, thereby preventing distant metastases. Surgery is performed 6–8 weeks after the radiochemotherapy. The addition of chemotherapy to radiotherapy improves local tumour control but also increases the risk of toxicity [32 34].

Chemotherapy

The chemotherapeutic drugs used for colorectal cancer include one old and well documented agent combined with a vitamin, two newer more efficient, but more toxic agents plus three new

targeted drugs. The old and most frequently used agent is 5-FU/folinic acid, with relatively limited acute side effects and no late adverse effects. The newer drugs are oxaliplatin and irinotecan which are used in combination with 5-FU. Oxaliplatin is used in the neoadjuvant, adjuvant, and palliative setting, and irinotecan is indicated for pallitive purposes. The *targeted drugs* are antibodies that inhibit the epithelial growth-factor receptor (cetuximab, panitumumab) or binds to vascular endothelial growth factor (bevacizumab). They are indicated for palliative purposes, where a limited effect on survival is reported [210 248 249]. However, the results from randomized trials evaluating the effect of *targeted drugs* in the adjuvant setting are disappointing, and they are not recommended for adjuvant treatment of stage II–III colorectal cancer [13 252].

Several randomized studies have reported a decreased risk of recurrence after colon cancer resection using adjuvant chemotherapy. Treatment with 6 months of postoperative 5-fluorouracil (5-FU)/folinic acid reduces the relative risk of recurrence by 30% [155 168 268]. Survival is increased nearly to the same extent. Adding oxaliplatin to 5-FU/folinic acid reduces the risk of recurrence by another 10-15% [14 100 273]. However, chemotherapy is associated with negative and sometimes severe or fatal side effects. For example, persistent peripheral sensory neuropathy is a troublesome toxicity associated with oxaliplatin [14 273].

Adjuvant chemotherapy is recommended for stage III and ”high-risk” stage II colon cancer patients, as the risk of recurrence is high (30–50%) [2 73 138]. Risk factors include few examined lymph nodes, poor histopathologic differentiation grade and, vascular, lymphatic, or perineural invasion, bowel obstruction or perforation, pT4 stage, and CRM involvement. The results for colon cancer have not been reproduced in rectal cancer, and the Swedish national guidelines do not recommend routine adjuvant chemotherapy for patients with rectal cancer outside clinical trials [2 32 41]. In patients with unresectable stage IV colon and rectal cancer, palliative chemotherapy prolongs survival [81 211].

Treatment of Liver Metastases

The definition of resectable liver metastases has changed over the years and now focuses on the resection of all visible liver metastases while preserving enough functional liver remnant with an adequate vascular supply and biliary drainage [8]. An increased use of improved neoadjuvant chemotherapy protocols allows tumour downsizing and consequent resection [10]. Advances in interventional radiology, in particular portal vein embolization and radiofrequency thermal ablation, have contributed to the management of patients with colorectal liver metastases [9 179]. The rapid development of treatment strategies and the importance of careful patient selection require evaluation by the MDT.

Treatment of Peritoneal Carcinomatosis

Cytoreductive Surgery and Peritonectomy Procedures

In 1980 Spratt et al. reported the use of combined surgical resections and heated intraperitoneal chemotherapy for the first time in a patient with pseudomyxoma peritonei [231]. Since then, CRS plus intraperitoneal chemotherapy has reached the level of gold standard treatment for colorectal carcinomatosis, pseudomyxoma peritonei, and peritoneal mesothelioma. CRS consists of numerous surgical procedures depending on the extent of peritoneal tumour manifestation. Sugarbaker provides detailed technical descriptions of the surgery which may include parietal and visceral peritonectomy, greater omentectomy, splenectomy, cholecystecomy, resection of the liver capsule, small bowel resection, colonic and rectal resection, gastrectomy, lesser omentectomy, pancreatic resection, hysterectomy, oophorectomy, and urinary bladder resection [235]. Above all, systematic exploration of all compartments and subsequent clearance of the peritoneal cavity is necessary to identify sites of disease. The aim is to obtain complete CRS. This goal needs to be weighed against the potential morbidity and functional results, with potential influence on the patient's quality of life. Frequently, implants on the small bowel surfaces are the major limitation to complete cytoreduction, since extensive small bowel resection is associated with a poor functional outcome (*Fig. 5*) [233]. The tumour found at the time of surgical exploration of the abdomen is quantified using the peritoneal cancer index (PCI) by Sugarbaker [194]. PCI comprises both the peritoneal implant size and distribution of the nodules on the peritoneal surface, and is valuable in assessment of prognosis and treatment planning in patients with PC (*Fig. 6*) [70].

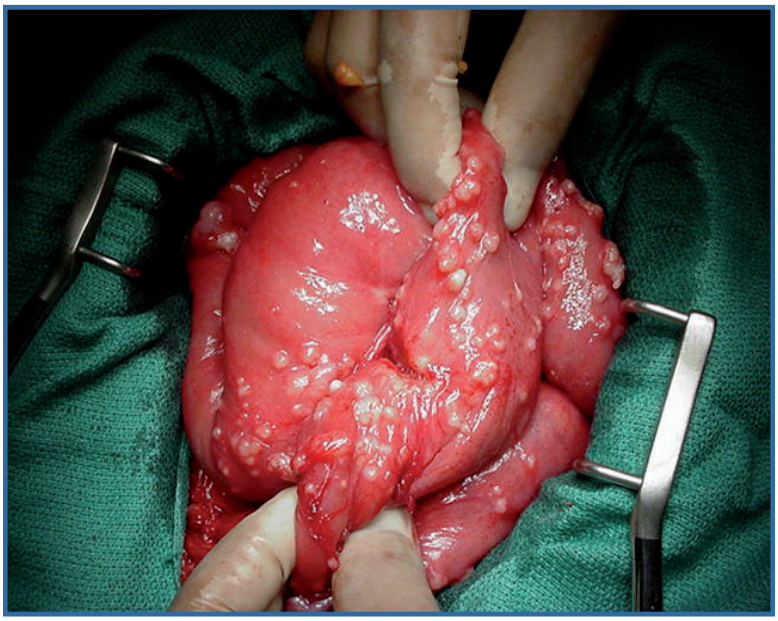
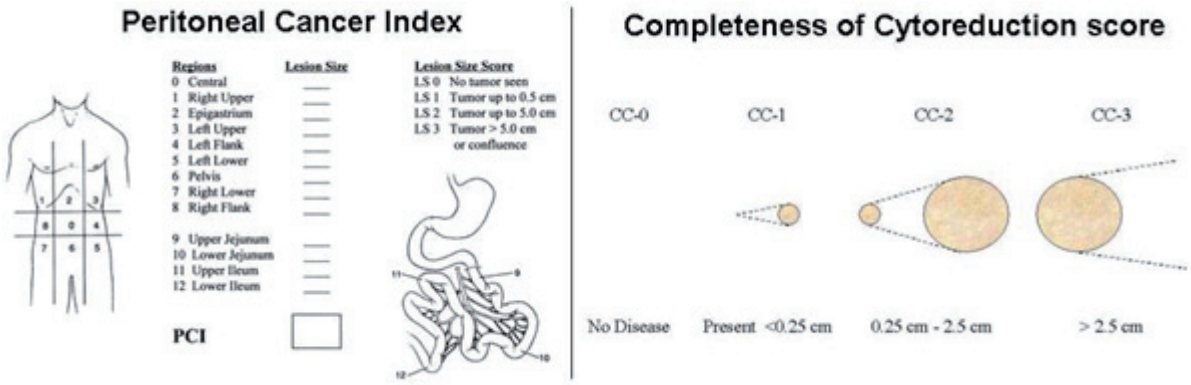


Figure 5. *Peritoneal carcinomatosis on the small bowel.*
With the kind permission of Dr Haile Mahteme

Laparoscopy may be performed to assess the extent of tumour growth on the small bowel and portal hepatis, in order to avoid laparotomy in patients where complete CRS is not feasible [82]. After CRS, the residual disease is classified intraoperatively using an established score. The completeness of cytoreduction (CC) score described by Sugarbaker is recommended in conformity with an experts' consensus [91]. Cytoreduction is considered to be adequate if either no macroscopic tumour remains (CC-0) or if only nodules less than approximately 2.5 mm (CC-1) remain to allow tumour penetration of intraperitoneal chemotherapy [64 119 234]. Median survival after inadequate cytoreduction is similar to that of palliative treatment only [208 258].



The abdomen and the pelvis are divided into 13 regions. The lesion size of the largest peritoneal implants are scored (0 -3) in each abdominopelvic region. They can be summated as a numerical score, which ranges from 0-39. The PCI is calculated at the time of surgical complete abdominal and pelvic exploration.

Figure 6. *Peritoneal carcinomatosis index and Completeness of Cytoreduction score*
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Intraperitoneal Chemotherapy

Cytoreductive surgery can be combined with hyperthermic intraperitoneal chemotherapy (HIPEC), early postoperative intraperitoneal chemotherapy (EPIC) or sequential postoperative intraperitoneal chemotherapy (SPIC), the first being the most common and standard today [46]. The pharmacokinetic rationale of intraperitoneal drug administration is based on the dose intensification that occurs because drug movement from the peritoneal cavity to plasma (peritoneal clearance) is generally slow relative to drug clearance from the body [64 119]. This results in a higher concentration in the peritoneal cavity compared with plasma after intraperitoneal administration [63].

There are many variations in exposure techniques (i.e. open or closed wall), duration (30 to 120 minutes), intraperitoneal temperatures (40 to 44 ^{o}C), type of perfusate, and flow rates [70].

Most groups use a drug dose based on calculated body surface area which is an accurate predictor of drug metabolism, and in this regard is a useful predictor of systemic toxicity [205]. Drugs selected for HIPEC are generally cell cycle phase-non-specific agents, characterized by a direct

cytotoxic effect and synergistic antitumoural activity with hyperthermia. Specific pharmacokinetic features, such as high molecular weight and water solubility, favour a prolonged retention of the drug in the peritoneal space and a low systemic absorption and toxicity profile, which is expressed by the favourable ratio between peritoneal and plasma concentrations. The most widely used drugs for colorectal PC are oxaliplatin, irinotecan, mitomycin C, cisplatin, and mephalan [229]. The main Swedish centre that performs CRS and HIPEC for colorectal carcinomatosis uses a regimen of oxaliplatin and irinotecan. Patients also receive concomitant intravenous 5-FU and folinic acid [251]. The open abdomen "Coliseum" technique is used to administer HIPEC and the duration of perfusion is 30 minutes (*Fig.7*) [213].

Adding hyperthermia to intraperitoneal chemotherapy may increase tumour response by several mechanisms. First, heat alone has a direct antitumour effect [120]. Mild hyperthermia of more than 41°C induces selective cytotoxicity of malignant cells. Second, mild hyperthermia augments the cytotoxic effects of some chemotherapeutic agents [21 135 170]. Third, experimental data suggest that hyperthermia may increase the penetration depth of the chemotherapy solution into tissues and tumour nodules [114].

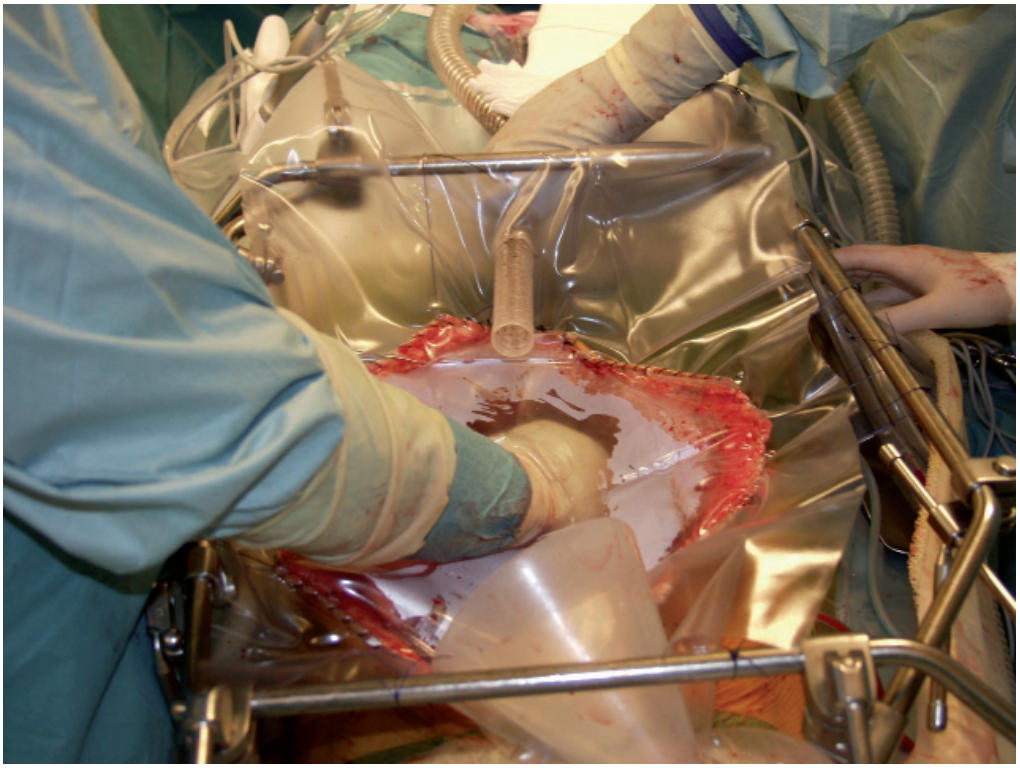


Figure 7. *Hyperthermic intraperitoneal chemotherapy administered with the"Coliseum" technique.*
With the kind permission of Dr Haile Mahteme

Indications and Contraindications

Many selection criteria have to be assessed in each patient: performance status, comorbidity, response to previous chemotherapies, histology grading, presence of extraabdominal or liver metastases, small bowel involvement and tumour volume assessed by the PCI. Combined resection of liver metastases with CRS and HIPEC has not been shown to influence survival in several studies [216] [253]. However, in a large multicenter study, liver metastases did have a negative prognostic influence in patients who had undergone complete CRS, which is the most important prognostic factor [70]. Other prognostic factors are the extent of PC, the experience of the center, the lymph node status, and adjuvant chemotherapy.

Second Look

Some authors advocate second-look surgery and HIPEC in an attempt to diagnose and treat PC at an early stage in high-risk patients [71] [153]. Two ongoing randomized controlled studies are evaluating this concept [50] [202]. Twelve months after resection of the primary tumour or after six months of adjuvant chemotherapy, patients who remain without evidence of colorectal cancer by imaging, physical examination and tumour markers are randomized to second-look surgery or standard-of-care surveillance. At laparotomy, all previous dissection planes are opened. If PC is detected, CRS and HIPEC are performed. When selecting patients with a possible benefit from second-look surgery and HIPEC, a knowledge of the epidemiology and risk factors of PC is essential.

Morbidity and Mortality

The morbidity and mortality seen in connection with CRS and HIPEC is reported to decrease with increasing experience [172]. In centers with an experience of more than 200 procedures, the reported major morbidity and mortality rates are about 20% and 2% respectively [88] [134] [237]. Major morbidity involves complications of surgery: anastomotic leakages, intraperitoneal sepsis, and hemorrage. Independent factors influencing morbidity are duration of surgery, extent of carcinomatosis, the number of anastomoses performed, and incomplete CRS. The main morbidity from HIPEC is haematological toxicity, which is reported to occur in 8–31% of patients.

The Role of Oophorectomy

Oophorectomy

In the case of macroscopic ovarian metastases, bilateral salpingo-oophorectomy (SOEB) is advised even if ovarian metastasis is diagnosed unilaterally, since ovarian involvement is likely to be bilateral [174] [240]. Ovarian metastases are common in patients with PC, and SOE could be considered in patients undergoing CRS and HIPEC even when there is no macroscopic evidence

of tumour [74]. However, in the main Swedish center that performs CRS and HIPEC, SOEB is not performed if the ovaries are without signs of disease.

Routine prophylactic SOE in order to prevent ovarian metastases has previously been recommended, but this has been debated [20 25 93]. The procedure lacks scientific support, and it is not recommended in national guidelines today [178 225 243]. In the only randomized trial on prohylactic oophorectomy in women with colorectal cancer, no microscopic ovarian metastases were found in any of the 77 patients with macroscopically normal ovaries randomized to oophorectomy [274]. Benefits of the procedure are a reduced risk of primary ovarian cancer, resection of possible microscopic synchronous ovarian metastases, and prevention of the development of metachronous ovarian metastases. The side effects are premature menopause in premenopausal women and an increased risk of androgen insufficiency in women of all ages. SOEB will reduce the serum levels of testosterone (T) by half and may be associated with sexual problems and a decrease in psychological well-being [61 76 143]. Furthermore, SOE is a risk factor for osteoporosis, cardiovascular disease, and death [52 56 164 185 232].

Risk of Primary Ovarian Cancer

The impact of radiotherapy for rectal cancer as a risk factor for secondary cancers has been analysed in some studies [24 126]. The results are divergent. An increased risk of second malignancies mainly within or adjacent to the irradiated volume was reported in a large cohort study. Another population-based cohort study reported a decreased risk of cancer of the prostate and an increased risk of cancer of the uterine cervix and corpus. No increased risk of primary ovarian cancer was seen in either of these studies.

Primary ovarian cancer is diagnosed in about 2% of the Swedish female population, with the highest incidence in women aged 60–64 years [226]. The risk is increased in women with breast-ovarian cancer syndrome (BRCA 1/2 mutation), with a cumulative risk for ovarian cancer at the age of 70 of 35–60% and 10–27%, respectively [124]. In patients with hereditary non-polyposis colorectal cancer syndrome (HNPCC), the life-time risk of ovarian cancer is 7–12%, with a median age at diagnosis of 40–47 years [7 129 254]. In these patients, prophylactic SOE is an important component of ovarian cancer risk reduction [124 129]. Furthermore, SOE before menopause reduces the risk of breast cancer in women with BRCA1/2 mutation as well as in the general population [125 184 199].

Sexual Function and Colorectal Cancer

As the prognosis of colorectal cancer has improved, interest has shifted to include quality of life and late effects of the cancer and its treatment. In general, descriptive cross-sectional and longitudinal studies among colorectal cancer survivors have concluded that the overall health-related quality of life after treatment is good [16 180 197]. However, previous studies have identified several sexual dysfunctions experienced by colorectal cancer survivors. Among men, these

include erectile dysfunction and ejaculatory disorders [104 158 244]. Among women, specific sexual dysfunctions include dyspareunia, impaired sexual desire, arousal, lubrication, and orgasms [104 108].

Moreover, relatively non-specific problems such as descreased level of sexual activity, lack of sexual enjoyment, and changes in body image have been identified in both men and women following treatment for colorectal cancer [96 218]. Sexuality and intimacy are considered central to a person's well-being and are important aspects of the quality of life [103]. Poor sexual functioning and reduced sexual satisfaction are risk factors for a worse quality of life in cancer survivors [28].

In rectal cancer patients, preoperative radiotherapy, advanced age and complications to surgery are risk factors for postoperative sexual dysfunction [108 142 158 242]. The type of surgery, presence of a stoma and low rectal tumours may also be associated with sexual dysfunction [108 116 242]. While male sexual dysfunction after rectal cancer treatment has been well described, considerably less data have been published about the impact on women [244]. Methodological limitations, such as retrospective study design, small sample size, or lack of validated assessment tools, are common.

Complications from radiotherapy for rectal cancer were described earlier (page 24). In men with rectal cancer treated with radiotherapy, subnormal serum levels of testosterone indicate permanent testicular dysfunction [38 40 272]. In women, vaginal fibrosis, dryness and bleeding may result from pelvic irradiation as well as decreased sexual arousal due to altered blood flow and denervation, infertility, and premature menopause [23 203].
In both pre- and postmenopausal women, radiotherapy for rectal cancer may reduce ovarian androgen production, but there is scant information on this in the literature. Female androgen insufficiency is associated with sexual dysfunction, reduced psychological well-being, and negative metabolic effects [60 78]. As such, androgen insufficiency could be a contributing factor to sexual dysfunction in women treated for rectal cancer.

Assessment of Sexual Function in Women

Questionnaires, structured interviews, daily rating scales or log books have all been used to evaluate female sexual function and dysfunction. There is, however, a lack of standardized, internationally acceptable questionnaires that are validated in general populations and can be used in women with or without disease and a sexual partner.
In colorectal cancer patients, the most frequently used questionnaires for evaluation of different aspects of quality of life, including sexual function, are the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ) [244]. In the colorectal cancer-specific QLQ-CR38 as well as the recently updated version, QLQ-CR29, evaluation of sexual problems is limited to women who have had intercourse in the last four weeks [230 261]. In the QLQ-CR29, only two items address sexual function.

The Female Sexual Function Index (FSFI) is a questionnaire composed of 19 multiple-choice items designed to assess the multidimensional nature of female sexual function (*Appendix*) [204]. Scores are calculated for six domains: sexual desire, arousal, lubrication, orgasm, satisfaction and dyspareunia. The domain scores can be summarized to a total score ranging from 2 to 36. An FSFI total score below 26.5 is considered to be pathological [262]. The FSFI has been validated to measure sexual function in sexually active women [165 204]. It was originally developed for pharmacological clinical trials, but it has been used for a large number of clinical conditions, including colorectal cancer [30 108 116]. In a review of 27 questionnaires addressing female sexual dysfunction, the FSFI reached the highest level of utility in clinical and research settings [86].

Data on objective measurements of the genital physiological response are limited. Photoplethysmography has been used to measure local blood flow in the vagina in order to assess genital arousal [136 137 191]. This instrument has been used after pelvic surgery, including a small prospective study on laparoscopic restorative proctocolectomy for ulcerative colitis or familial adenomatous polyposis (FAP) syndrome [266]. A significant postoperative reduction in vaginal vasocongestion measured during sexual stimulation was reported. However, subjective sexual arousal, estimated lubrication, and sexual functioning were not diminished.
MRI measurement of clitorial volume has been used to evaluate genital arousal during exposure to erotic film. An increased clitorial volume was reported in healthy subjects [66]. The method has also been used to evaluate response to siladenfil administration in women with female sexual arousal disorder [271].
The new technology of thermography measuring infrared radiation has suggested that labial temperature change is correlated to sexual arousal [133].

Ovarian Function and Androgen Production

The main androgens in women, listed in the descending order of their serum concentrations, include dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (A-4), testosterone (T), and dihydrotestosterone (DHT). DHEAS, DHEA, and A-4 are regarded as pro-androgens since they require conversion to testosterone or DHT to show androgenic effects in target tissues [220]. Androgen biosynthesis takes place in the adrenals and ovaries. Testosterone is produced mainly by the interstitial cells of the ovary, DHEAS by the adrenal cortex, and DHEA and A-4 are produced by both the ovary and adrenal cortex. In peripheric tissues, testosterone is converted to DHT, the principal ligand for androgen receptors. Androgens are also precursor hormones for estrogen production in the ovaries of premenopausal women and for conversion to estradiol in peripheric tissues in both pre- and postmenopausal women [54]. Androgen levels decline with age in adult women [42 95]. In a large, cross-sectional study, testosterone levels in women declined steeply from age 18 to 34 years, with a more gradual decline in levels until a nadir in the mid-60s [61]. The pattern was similar for A-4 and DHEAS. The decline is probably mainly a consequence of reduced adrenal production and not of natural menopause as the post-menopausal ovary is an ongoing site of testosterone production [11 42].

Only 1–2% of total circulating testosterone is free, while around 25% is weakly bound to albumin and the remainder is strongly bound to sex hormone-binding globulin (SHBG) [255]. Only the free fraction of T is biologically active.

The reference limit for total T in women is <2.5–3 nmol/litre. However, there is no defined cut-off level defining T insufficiency. Etiologic factors associated with androgen insufficiency in women include:

1. Ovarian (chemotherapy, irradiation, oophorectomy) [61 113 143]
2. Adrenal (adrenal insufficiency, adrenalectomy)
3. Hypothalamic-pituitary (hypopituitarism)
4. Drug-related (GnRH agonists/antagonists, corticosteroids, oral contraceptives, oral estrogen treatment) [51]
5. Idiopathic

According to a consensus statement, no commercially available assays are sufficiently sensitive or reliable for the low androgen levels in women [18]. It was concluded that total androgen production is best reflected by the total testosterone concentration, and that it is necessary to consider SHBG levels in the assessment of bioavailable testosterone in women.

Role of Hormones in Female Sexual Function

Androgens

Although hormones play an important role in female sexual function, it has been difficult to show correlations between endogenous levels and various aspects of sexuality. This probably reflects the complexity and many factors (physiological, psychosocial, cultural) involved in female sexuality. Animal and human data suggest, however, that testosterone directly influences sexual behaviour and libido via androgen receptors in the CNS [83 163]. Androgens are also involved in the genital physiological response through regulation of the smooth muscle and local blood flow [246]. Increased vaginal blood flow after visual erotic stimulation has been demonstrated after sublingual testosterone administration [247]. A direct effect of this increased vasocongestion is lubrication, as pressure in the small vessels of the vaginal wall increases and plasma transudate passively flows through the epithelium [76]. Damage to autonomic nerves disrupt this process [22 200]. Inadequate sexual arousal may be partly due to decreased blood flow to the sexually responsive organs. Testosterone has been considered to be the key hormone in sexual desire in both men and women. In several studies, exogenous testosterone has been shown to increase levels of sexual desire in premenopausal women and women after surgical or natural menopause [36 59 77 217]. A Cochrane review concludes that the addition of testosterone to postmenopausal hormone replacement therapy (HRT) improves desire, arousal and other aspects of female sexual dysfunction [228]. A small number of studies report a direct relationship between serum levels of endogenous testosterone and sexual desire and coital frequency [12 19 187 201]. However, other studies exploring the relationship between endogenous androgens and

sexual function have shown conflicting results [68 92 212]. In the largest study exploring this relationship, no correlation was found between low scores in any of the sexual domains evaluated and low serum levels of total testosterone, free testosterone, or A-4 [60].

There is still much controversy and insufficient knowledge about Female Androgen Insufficiency (FAI) [4 35 245]. In 2002, a Consensus Conference on androgens agreed that androgen insufficiency in women with adequate estrogen levels could lead to a diminished sense of well-being and energy, fatigue, and decreased sexual desire [18]. A more recent position statement recommended against making a diagnosis of ”androgen insufficiency”, because of the lack of a well-defined clinical syndrome and normative data across the lifespan [263].

Estradiol

There is consistent evidence for the importance of estradiol for normal vaginal lubrication. Estradiol deficiency after surgical or radiotherapy-induced menopause results in an atrophic vaginal epithelium which causes coital pain. The physiological post-menopausal reduction in estradiol is frequently associated with vaginal dryness, which improves with estradiol replacement [207]. In addition, improved sexual function, feelings of well-being, and mood have been reported following estradiol therapy in women with menopausal symptoms [62 67 177].

Aims of the Thesis

The aims were to assess

- the effects of development and implementation of MDT assessment and treatment in patients with stage IV colon and rectal cancer

- the incidence, prevalence and risk factors for colorectal peritoneal carcinomatosis (PC)

- the incidence, prevalence, clinical characteristics and prognosis of ovarian metastases in women with colorectal cancer

- feasibility and internal and external validity in an ongoing prospective study on sexual function and androgen levels in women with rectal cancer

Patients and Methods

Papers I-III are large population-based cohort studies including patients from the Regional Quality Registry for Colorectal Cancer. Paper IV is an analysis of bias and baseline data in prospective observational cohort study with ongoing inclusion of patients from multiple institutions. The origins of the cohorts and the number of patients in each study are presented in *Table 4*.

Table 4. Patients included in the studies

Paper	Inclusion period	Follow-up until	Origin of the cohort	Study cohort	Number of patients
I	1995/96–2004	2006	All inhabitants in the Stockholm region	All patients with stage IV colorectal cancer	1449 patients
II	1995/96–2007	2010	All inhabitants in the Stockholm region	All patients with colorectal cancer of all stages	11.124 patients
				Outcome analysis; patients who had abdominal resection of a primary colorectal cancer stage I–III and who were alive 30 days postoperatively	7799 patients
III	1995/96–2006	2008	All inhabitants in the Stockholm region	All women with colorectal cancer of all stages, without previous or synchronous gynaecological cancer	4566 female patients
				Outcome analysis; patients who had an R0 resection of a stage I–III colorectal cancer and who had not undergone bilateral oophorectomy	2852 female patients
IV	June 2008 – June 2011	Only baseline data	All 237 women with rectal cancer treated at any of the participating institutions.	Eligible women scheduled to undergo abdominal surgery for stage I–III rectal cancer who consented to join the study	82 female patients

The Regional Quality Registry

The Stockholm Colorectal Cancer Study Group was set up in 1980. The group consists of surgeons, radiologists, oncologists and pathologists representing all the hospitals in the Stockholm-Gotland region. The aim is to improve outcome in patients with colorectal cancer. As a part of this, treatment guidelines and a Regional Quality Registry have been established. Clinical and pathological data have been logged prospectively in the Registry since 1995 (rectal cancer) and 1996 (colon cancer). The Registry covers 100 % of the colorectal cancer patients in the region, according to the National Cancer Registry. The Regional Quality Registry includes detailed clinical data on patient and tumour characteristics, treatment of the primary tumour and follow-up. Up to three different locations of metastases can be registered in the database. From 2007 onward, additional information on, for example, ASA classification, subclassification of T4 stage, information on MDT assessment before and after surgery and open or laparoscopic surgery is also recorded. In addition to follow-up data from planned check-ups, unexpected events such as local recurrences or metachronous metastases are recorded. The register is frequently used in research projects and is regularly validated by cross-checking medical records, histopathology reports, and other registries (the Swedish Cancer Registry, the Cause of Death Register and the Stockholm County Council Registry).

The Stockholm County Council Registry

This registry covers the in- and outpatient healthcare consumption of all 2.1 million inhabitants in the region and includes healthcare provider, length of hospital stay, diagnoses according to the International Classification of Diseases, and type of surgery performed.

Paper I

The study population consists of patients with stage IV colorectal cancer at diagnosis. Patients with tumours diagnosed at autopsy were not included. Information was taken mainly from the Regional Quality Registry. At the time of the study period, data on MDT assessment were not included in the Registry. Therefore, this information was taken from the Stockholm County Council Registry and was checked individually for every patient. An MDT conference was defined as a structured discussion of treatment strategies between at least a surgeon and an oncologist before or after surgery. Medical records were reviewed for patients who had additional operations and for patients treated postoperatively with RT. Surgical treatment includes resection of the primary tumour, and, in patients where the primary tumour was not resected, diverting stoma, enteroanastomosis, or laparotomy only. Surgical procedures performed in other regions were not registered. The colon and rectal cancer patients were categorized into four different treatment groups according to resection of the primary tumour and surgery for metastases, and data were analysed separately for these groups. Data were also analysed separately for the periods 1995–1999 and 2000–2004.

Paper II

This study included patients with all stages of colorectal cancer. Patients with tumours diagnosed at autopsy were included in the study cohort. Data were obtained from the Regional Quality Registry. In certain patients data were validated against the Stockholm County Council Registry, medical records and/or histopathology reports. This validation was performed in patients with perforated primary tumours, ovarian and small bowel metastases, primary ovarian cancers, local recurrences, metastases in three different locations excluding PC, if three year follow-up data were missing or if the patient had died without any reported metastases or recurrences.

In the risk factor analysis, all patients alive 30 days after resection of a stage I–III colorectal cancer were included.

Peritoneal carcinomatosis was defined as micro- or macroscopic tumour growth in the peritoneum or ascites containing cancer cells. Intra-abdominal local recurrences with tumour growth in the peritoneum were also defined as PC. Anastomotic or retroperitoneal recurrences or stage T4 tumours with serosal involvement or overgrowth on adjacent organs without separate peritoneal metastases were not defined as PC.

All cytoreductive surgery (CRS) combined with intraperitoneal chemotherapy during the study period was performed at the same referral center. The first patient from the study cohort was treated in 1999. Surgery was combined with sequential postoperative intraabdominal chemotherapy until 2003. Thereafter, HIPEC became standard.

Paper III

This study included women with colorectal cancer of all stages, without a previous or synchronous history of gynaecological cancer. Patients with primary tumours diagnosed at autopsy were included in the study cohort. Medical records and histopathology reports were reviewed for patients who had ovarian metastases, ovarian cancer, and for patients with missing follow-up data. The diagnosis of ovarian metastases was confirmed by histopathology in at least 75 of 79 patients.

In the analysis of the incidence of metachronous ovarian metastases, patients who underwent bilateral oophorectomy at the primary operation were not included as they were no longer at risk.

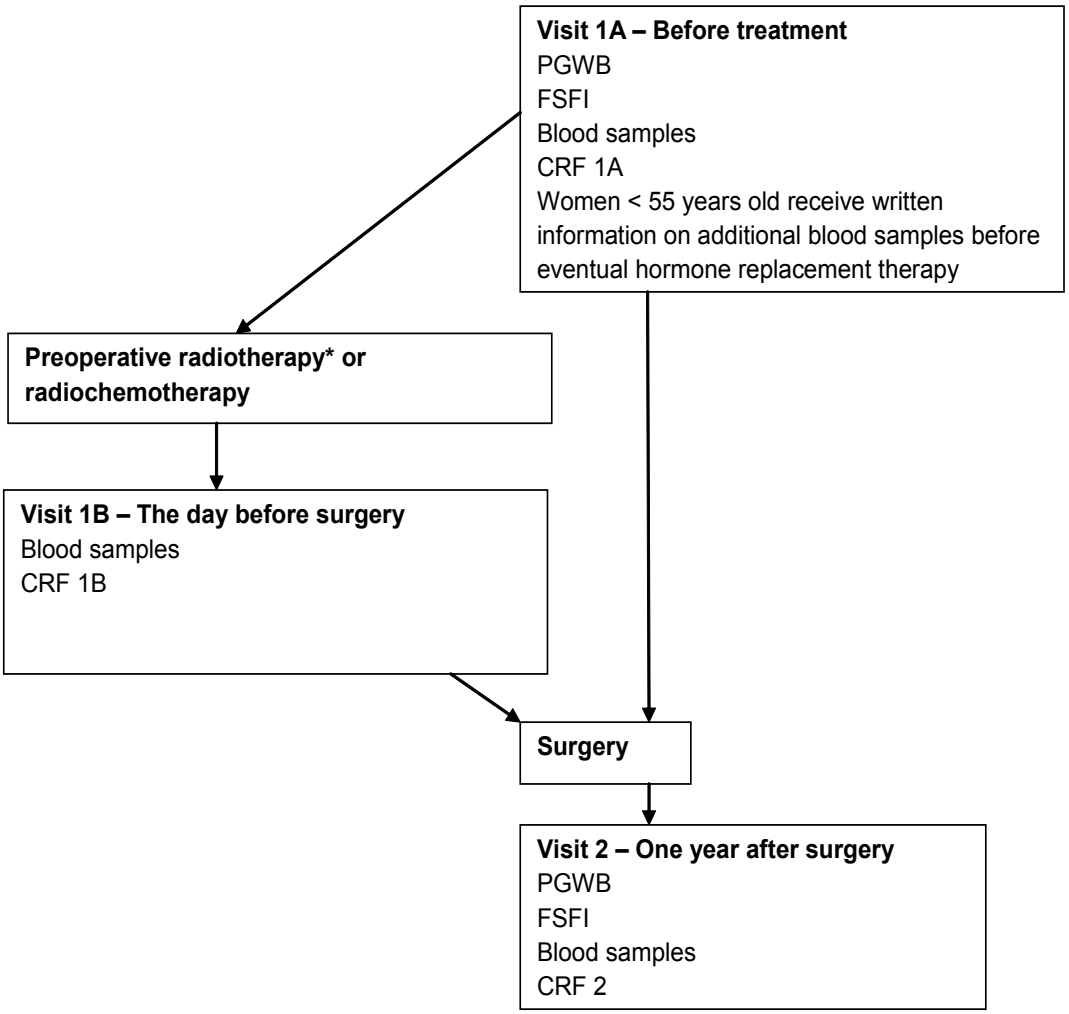
Data were analysed separately for patients with colon and rectal cancer who had undergone a ”curative” resection, i.e. an R0 resection of a stage I–III tumour. These data were presented only for women with colon cancer, as metachronous ovarian metastases were very uncommon in those with rectal cancer. Patients were allocated to one of three groups (no recurrence, ovarian metastases and any other recurrence), and data for these groups were analysed separately.

Paper IV

Women with rectal cancer were included at four high-volume centres for rectal cancer surgery. The study design of the prospective, ongoing study is described in *Fig. 8*. The primary endpoint is sexual function after treatment, measured using the FSFI- questionnaire, described on page 33 [204]. Secondary endpoints are psychological well-being, hormone levels after treatment and possible correlations between sexual function and androgen levels. When the study was planned, no normative FSFI data for women of the same age group were found in a PubMed search of the literature. Therefore, a previously performed power analysis based on FSFI data from younger women was used and in addition, a power analysis of a secondary endpoint, testosterone levels after radiotherapy, was performed. The estimated patient cohort size required to detect a significant treatment-related effect on the mean total FSFI score was 60–80 women. Inclusion criteria were women scheduled to undergo abdominal surgery for stage I–III rectal cancer. Exclusion criterion was inability to give informed consent.

When the initially planned sample size was reached, the question was raised as to whether this would actually be sufficient to demonstrate a measurable significant postoperative reduction of the mean total FSFI score, or if a larger sample size would be needed. Moreover, since a large proportion of eligible women were not included in the study, the possibility of a selection bias for those included had to be assessed.
In paper IV feasibility and internal and external validity were assessed. Women in the study cohort were compared with those who were eligible for inclusion, but not included, with regard to clinical data and treatment. These data were obtained from the Swedish Rectal Cancer Registry. In the study cohort, sexual function was measured using FSFI, clinical data were collected, and blood samples were drawn. To avoid any negative influence of the recently diagnosed cancer on the pre treatment questionnaires, patients were asked to answer according to their situation before they experienced symptoms from the tumour. The FSFI scores were calculated irrespective of whether the women were sexually active or not. Domain scores were calculated for patients with complete responses in the corresponding items, and total scores were calculated for patients with complete responses in all items.

In the final study, analysis of several biomarkers will be performed according to the study design (*Fig. 8*). In the present study, serum was analysed for total T, sex hormone-binding globulin (SHBG), and plasma levels of albumin. In women under 55 years old, serum was analysed for reproductive hormones. Concentrations of free T were calculated from values for total T, SHBG, and albumin concentrations by successive approximation using a computer program based on an equation system derived from the law of mass action [227]. Clinical data and T levels were compared for women who did and who did not complete all FSFI items. A new power analysis based on FSFI total scores of the first 82 patients included was performed.



Serum or plasma analyses:

1. Androgens: Total testosterone (T), sex hormone-binding globulin (SHBG), androstenedione (A-4), dehydroepiandrosterone-sulphate (DHEAS)
2. Thyroid and parathyroid function: thyroxine (T-4), thyrotropin (TSH), parathyroid hormone (PTH), calcium, albumin
3. Cortisol
4. Anabolic function: Insulin-like growth factor 1 (IGF-1), Insulin-like growth factor binding protein 1 (IGFBP-1), Insulin-like growth factor binding protein 3 (IGFBP-3)
5. Bone markers: osteocalcin, carboxyterminal telopeptide of type 1 collagen (1CTP), carboxyterminal propeptide of type 1 procollagen (P1CP)
6. Women < 55 years old: oestradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone, anti-mullerian hormone (AMH)

*Three possible radiotherapy regimens:
5x5 Gray + operation within one week
5x5 Gray + operation after four to eight weeks
25x2 Gray + operation after four to eight weeks

Figure 8. *Design of the prospective study on sexual function and androgen levels in women with rectal cancer.*

Statistical analysis

Papers I–IV

Distributions were compared using the χ^2 test of independence or Fisher's exact test, as appropriate. Continuous variables such as age, time, and laboratory data were compared using the Mann-Whitney U test or the Kruskal-Wallis test. All tests were two-sided and p values below 0.05 were considered statistically significant.

In the analysis of event-specific rates, patients were considered to be at risk for the studied event until death or the end of follow-up. Survival and the cumulative incidence were estimated using the Kaplan Meier method and the differences were assessed by the log-rank test. Cox proportional hazards regression was used to model the risk of not being assessed by the MDT with respect to potential confounding factors and to model the incidence of diagnosed metachronous PC with respect to different covariates. Results are presented as hazard ratios (HRs) or odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

Ethics

All studies were approved by the Regional ethical review boards.

Results and Discussion

Paper I

Differences in Multidisciplinary Team Assessment and Treatment between Patients with Stage IV Colon and Rectal Cancer

In all, 7894 patients were included in the Regional Quality Registry during the study period. In 1000 patients with colon cancer and 449 with rectal cancer, metastases were found at the time of diagnosis (study cohort). Of these, 689 (68.9%) colon cancer patients and 352 (78.4%) rectal cancer patients were assessed by an MDT and the proportion increased over the study period ($P < 0.001$). Surgery for metastases was done on 39 (3.9%) colon cancer patients and 38 (8.5%) rectal cancer patients ($P < 0.001$). Colorectal cancer patients selected for metastasis surgery had 37% 5-year survival compared to 2% in patients not selected for metastasis surgery ($P < 0.001$).

Surgery

In the majority of the patients, the primary tumour was resected (722 of 1000 (72.2 %) in colon cancer patients *vs* 295 of 449 (65.7 %)($P = 0.012$) in rectal cancer patients). In elective resections of the primary tumour, local tumour clearance was complete in 373 of 506 (73.7 %) colon cancer resections and 191 of 283 (67.5 %) rectal cancer resections ($P = 0.063$). For emergency resections, the corresponding figures were 133 of 216 (61.6 %) and 5 of 12 (41.7 %), respectively ($P = 0.240$).

There has been a shift to a more conservative management of the primary tumour in patients with disseminated disease where curative surgery is not possible. Palliative chemotherapy without surgery is often adviseable if there are no or only mild symptoms from the primary tumour. Palliative radiotherapy is sometimes indicated for rectal cancers. However, surgery with a diverting stoma, enteroanastomosis, stent or resection of the primary tumour may be neccessary in the case of bleeding, perforation, or obstruction. Careful evaluation and treatment planning in an MDT setting can help to avoid the morbidity of a surgical procedure with dubious benefit. According to 2009–2010 data from the Swedish Colon and Rectal Cancer Registries, 66.8% *vs* 8.6% of stage IV colon and rectal cancers are resected [5 6]. In an international study on rectal cancer management, departments with regular MDT meetings were more likely to treat synchronous liver metastases with new neoadjuvant chemotherapy and to avoid one-stage surgery of liver metastases and primary tumours [17].

Multidisciplinary Team Assessment

A smaller proportion of patients with colon cancer was assessed by the MDT: 68.9% *vs* 78.4% for those with rectal cancer. The proportion of MDT-assessed patients increased over the study period, from 58.6% to 76.3% for patients with colon cancer ($P < 0.001$) and from 72.4% to 83.7% for patients with rectal cancer ($P = 0.005$), as shown by comparison of patients from 1995 to 1999 *vs* those from 2000 to 2004. Improved oncological treatment and ongoing trials evaluating new chemotherapeutic drugs may have contributed to this increase in MDT assessment over time. However, we used a wide definition of the term. During the early years of the study period, the MDT assessment was usually a structured discussion of treatment strategies involving just a surgeon and an oncologist. This has developed into today's conferences where colorectal surgeons, a radiologist, an oncologist, a pathologist, specialized nurses, and occasionally a liver surgeon are present. According to the Department of Health in the United Kingdom, an MDT is defined as a "group of people of different healthcare disciplines, which meets together at a given time (whether physically in one place, or by video or teleconferencing) to discuss a given patient and who are each able to contribute independently to the diagnostic and treatment decisions about the patient" [140].The wide definition in Paper I reflects the difficulty to determine an exact date when MDT conferences were set up in each individual hospital in the region, as this has developed gradually in different ways, and reported differently to the registries. For example, in one hospital, the postoperative discussion with the pathologist step by step became a pre-and postoperative discussion with both pathologist and oncologist, and later on, the radiologist was involved. Another hospital started up with magnetic resonance imaging (MRI) conferences discussing rectal cancer patients preoperatively with the radiologist, and the oncologist at the same department was contacted when needed. The colon and rectal cancer patients were treated in ten different hospitals in the region, including two university hospitals. Liver surgeons have been present at the MDT conferences in university hospitals but not in others.

There may be several reasons why rectal cancer patients were more frequently assessed by the MDT than colon cancer patients in the current study. Above all, rectal cancer patients were younger and less frequently had surgery on an emergency basis. Another possible contributing factor is that, during the past three decades, there has been a focus in Sweden mainly on rectal cancer treatment with the addition of preoperative RT and the introduction of TME-based surgery [3 47 159 160].

In agreement with the present study, MDT assessment was more common in patients with rectal cancer than colon cancer in a population-based study from France [33]. In that study, other factors associated with MDT assessment were age < 75 years, diagnosis established in university hospitals, and advanced TNM stage. Overall, a multidisciplinary meeting was conducted for 32% of patients, with a wide variation between different geographical areas and types of hospitals. In the present study, factors associated with MDT assessment were age < 72 years, liver metastases only, and elective surgery. However, in this analysis, there is a risk of bias. For example, the most severely ill patients may be found in the "No surgery" group. If they die before the MDT conference takes place, the risk of not being assessed by the MDT is exaggerated for this group, since only living patients are discussed.

Surgery for Metastases and Survival

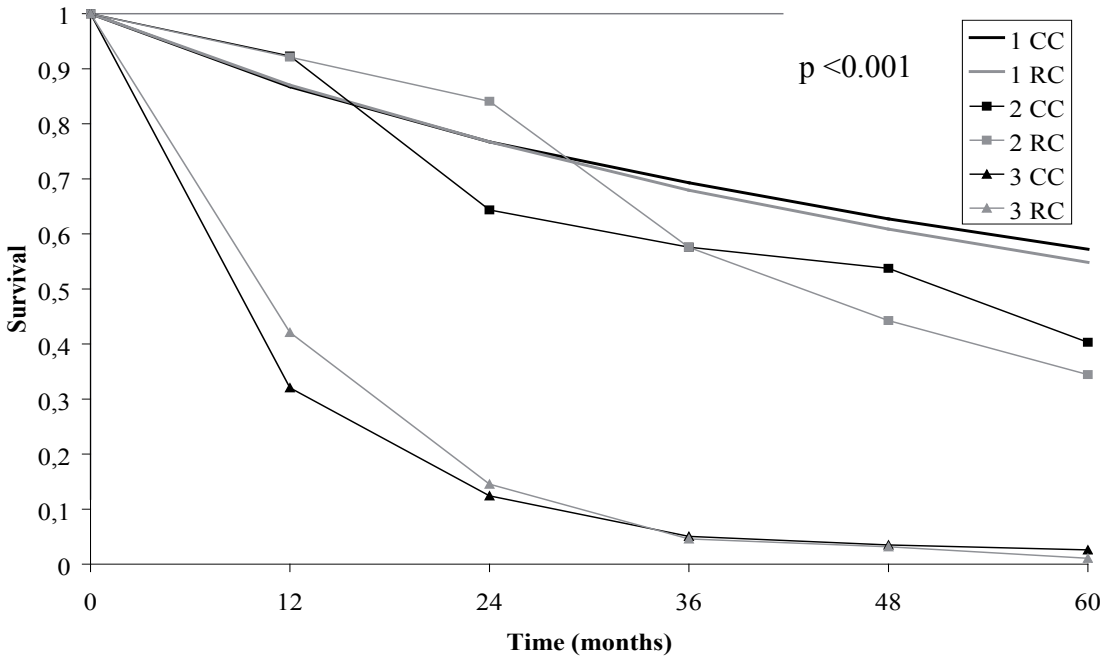
During the follow-up time, 39 (3.9%) patients with colon cancer and 38 (8.5 %) patients with rectal cancer had surgery for metastases ($P < 0.001$). The most common procedure was hepatic resection. In total, metastasis surgery was more common among patients who were assessed by an MDT than among patients who were not (72 of 1041 (6.9%) *vs* 5 of 409 (1.2%) ($P < 0.001$)). Surgery for metastases was more common in patients with colorectal cancers diagnosed during the second half of the study period than the first (20 of 628 (3.2%) *vs* 57 of 821 (6.9%) ($P < 0.001$)). Colorectal cancer patients selected for metastasis surgery had less extensive metastatic disease (data not shown) and were younger (63 (27 – 85) years *vs* 72 (23-97) years ($P < 0.001$)) than those who were not. As mentioned above, information on ASA classification or comorbidity was not available in the register for the study period, but one can assume that there were differences between groups.

The overall survival rate after five years in all patients with stage IV colorectal cancer was 4% compared with 56% in patients with stage I–III tumours diagnosed during the same time period ($P < 0.001$). In patients with stage IV disease selected for metastatic surgery, the estimated survival after five years was 37% (*Fig.* 9). The 5-year survival rate is higher than that reported in other population-based studies, which ranged between 10.8% and 27.9% after resection of synchronous colorectal liver metastases and 21.6% after resection of synchronous and metachronous colorectal metastases in all locations [55 97 146 156]. One study has reported an association between assessment in an MDT including a liver surgeon and improved overall survival in colorectal cancer patients with liver metastases [149]. Improved survival has also been reported for stage II–IV colorectal cancer patients after the inception of MDT conferences [150]. Moreover, implementation of MDT conferences has been shown to select more rectal cancer patients to neoadjuvant treatment, to lower the rate of CRM involvement, and increase local tumour control [43 183]. A positive association between MDT assessment and survival has also been reported for other malignancies in several studies [111].

In the current study, patients who were not assessed by the MDT ran a significantly higher risk of dying than patients who were, after adjustment for available possible influencing factors in a multivariate model. Unfortunately, this analysis may suffer from confounding and immortal time bias. If the MDT discussion influences treatment decisions, an effect on survival is expected. However, if for example, ASA classification was included in the analysis, the positive prognostic effect of the MDT would probably decrease as there is probably a selection of less severely ill patients to be discussed by the MDT. Furthermore, the time between cohort entry (= diagnosis) and exposure (= MDT conference) is clearly ”immortal time”, causing a bias, since the exposed subjects must survive this period to be discussed by the MDT. Thus, classifying this ”immortal time” as exposed time provides the MDT group with an artificial survival advantage over the unexposed subjects.

In summary, advances in radiological staging, improved surgical techniques, and an increasing complexity in radiotherapy and medical oncological treatment highlights the importance of the MDT assessment in both colon and rectal cancer patients in order to open up the opportunity for more aggressive treatment with better outcomes. Advanced age or emergency surgery is

no reason today to exclude patients with metastatic disease from an optimal treatment. MDT assessment is also important not least for patients whose only treatment option is palliative care: it saves unnecessary visits to oncologists and helps expedite contact with palliative care providers.



1=Stage I-III
2=Stage IV, resection of primary tumour and metastases
3=Stage IV, no metastasis surgery

CC: colon cancer; RC: rectal cancer

Figure 9. *Overall survival of patients with colorectal cancer according to stage and metastasis surgery.*

Paper II

Incidence, Prevalence and Risk Factors for Peritoneal Carcinomatosis from Colorectal Cancer – a Population Based Study

In all, 11.124 patients with colorectal cancer were included in the Regional Quality Registry during the study period. Nine hundred and twenty-four (8.3%) of these had synchronous or metachronous PC. PC was the first and only localization of metastases in 535 patients (4.8%). The prevalence of synchronous PC at the time of diagnosis of the primary tumour was 4.3% (477 of 11.124). The cumulative incidence of metachronous PC was 4.2% (447 of 10.646). Independent predictors for metachronous PC were age > 70 years, colon cancer, advanced T stage, advanced N stage, emergency surgery, and non radical resection of the primary tumour.

Previously, small retrospective follow-up studies published before the era of modern chemotherapeutics have reported metachronous PC in 2–19% after curative surgery [131]. More recently, Jayne et al. reported synchronous and metachronous PC in 7% and 4.5% respectively, in a retrospectively analysed series of 3019 patients with colorectal cancer treated at a tertiary referral centre for much of south-east Asia, which presents geographical problems for long term follow-up [117].

The present study on all patients with colorectal cancer in a large, geographically defined, population showed a prevalence of 4.3% for synchronous PC and a cumulative incidence during follow-up of 4.2% for metachronous PC. The thorough review of the registers and medical records probably identified most of the diagnosed cases of PC. Nevertheless, asymptomatic PC may have been missed since the intensity of follow-up has varied during the study period. PC may also not have been diagnosed in patients already diagnosed with disseminated disease, where the only treatment option is palliative. In addition, the autopsy rate was low during the study period [223].

Risk factors

Metachronous PC was found in 447 of 10.646 (4.2%) colorectal cancer patients. Uni- and multivariate analyses of risk factors for developing metachronous PC were performed for 7799 patients who underwent abdominal resection of a primary colorectal cancer stage I–III and who were alive 30 days postoperatively. Metachronous PC was diagnosed during follow-up in 380 of these patients (4.9%) after a median period of 16 (range 1.4 to 142) months after surgery. Independent predictors for developing metachronous PC were colon cancer, particularly right-sided, tumour stage T3 to T4, lymph node stage N1 to N2, less than 12 lymph nodes examined, emergency procedures, and non-radical resections of the primary tumour (R1 to R2). Patients > 70 years of age had a decreased risk of metachronous PC (*Table 5*). In the study by Jayne et al., liver metastases, tumour stage, nodal stage, and venous and perineural tumour invasion were independent predictors for the development of metachronous PC following curative resection [117]. Other suggested risk factors are limited PC at the primary operation, ovarian metastases and perforated or obstructive primary tumours [71 264].

Knowledge concerning predictors and time to recurrence is essential if early diagnosis of PC and aggressive treatment with curative intent is considered. Some authors advocate second-look surgery in patients at high risk of developing PC [71 145 169 236]. Two ongoing prospective randomized controlled trials evaluate second-look surgery with HIPEC and CRS versus standard-of-care surveillance in patients at high risk of developing colorectal PC [50 202]. In these studies, second-look surgery is performed either after six months of adjuvant chemotherapy or 12 months after the primary operation.

Prophylactic treatment using the HIPEC procedure to prevent development of PC is also being discussed for T4 carcinomas [256]. In the current study, the risk of metachronous PC was 10-fold higher after resection of a T4 tumour compared to T1. Among those with resected T4 tumours, 259 (27.8%) of 934 patients with colon cancer and 22 (10.8%) of 204 with rectal cancer were diagnosed with synchronous or metachronous PC (P<0.001). Subclassification of T4 stage was only available for tumours diagnosed during the last year of the study. In these patients, PC was more common in cases of tumour penetration to the surface of visceral peritoneum than in tumour invasion of other organs (20 of 71 *vs* 3 of 27) (P = 0.075) although this did not reach statistical difference. An association between local peritoneal involvement and PC for rectal cancer has previously been reported [167]. The increased risk for patients with T4 tumours could be taken into account when deciding upon follow-up regimens. In patients with several risk factors, in particular high T-stage, who are expected to tolerate CRS and HIPEC, a close follow-up with computed tomography and determination of CEA level would be appropriate. The value of second-look surgery with the possibility of CRS and HIPEC, or HIPEC concomitantly with resection of the primary tumour, remains to be determined.

Ovarian Metastases and Peritoneal Carcinomatosis

Ovarian metastases were more common in women diagnosed with PC and vice versa. Synchronous and metachronous metastases taken together, among all 98 women with ovarian metastases, PC was diagnosed in 64 women (65%). This is consistent with a cohort study on 103 women with synchronous or metachronous ovarian metastases from colorectal cancer, 52% of whom were diagnosed with synchronous PC [127]. In the current study, among the 483 women with PC, ovarian metastases were diagnosed in 64 (13%). This figure is less compared to a previous study reporting micro- or macroscopic ovarian metastases in 52% of 194 women undergoing CRS and HIPEC for peritoneal carcinomatosis of colorectal origin [74].

Survival

In total, 36 colon cancer patients and one rectal cancer patient from the cohort were operated on for PC at the referral center during the study period. The procedures performed were CRS in 26 patients, debulking surgery in eight patients and only laparotomy without resection in three patients. Surgery was combined with intraabdominal chemotherapy in all cases where resection was performed. The estimated median survival from diagnosis of PC in the 34 patients undergoing CRS or debulking surgery was 26.9 (95% CI, 18.3 to 31.5) months, which is

Table 5. Cox proportional regression analysis of predictors for developing metachronous peritoneal carcinomatosis in patients alive 30 days after abdominal resection of stage I–III colorectal cancer.

Predictor		No. of patients (n=7799)	No with PC	Multivariable analysis Hazard ratio	P
Age	< 49	367	28	1.2 (0.8–1.8)	0.003
	49–70	2662	162	1.0	
	> 70	4770	190	0.7 (0.6–0.9)	
Tumour site	Right colon	2366	149	1.8 (1.3–2.4)	0.002
	Transverse colon	523	26	1.2 (0.8–1.9)	
	Left colon	2273	129	1.5 (1.1–2.0)	
	Colon NOS	1	0		
	Rectum	2636	76	1.0	
Tumour status	T0 or T1	10+412	0+5	1.0	< 0.001
	T2	1423	8	0.6 (0.2–2.3)	
	T3	5285	261	3.8 (1.2–12.0)	
	T4	628	106	10.0 (3.1–32.1)	
	Data missing	41	0		
Node status*	N0 (≥ 12)	1696	36	1.00	< 0.001
	N0 (< 12)	2986	87	1.7 (1.2–2.6)	
	N1 (≥ 12)	629	32	2.2 (1.3–3.5)	
	N1 (< 12)	1115	86	3.8 (2.5–5.6)	
	N2 (≥ 12)	643	76	4.7 (3.1–7.1)	
	N2 (< 12)	424	54	7.4 (4.8–11.5)	
	Data missing	306	9		
Type of surgery	Elective	6843	270	1.0	< 0.001
	Emergency	956	110	2.1 (1.7–2.7)	
Radicality	R0	6864	254	1.0	< 0.001
	R1	224	31	2.0 (1.3–2.9)	
	R2	594	85	2.8 (2.1–3.6)	
	Data missing	117	10	1.2 (0.6–2.6)	
Adjuvant chemotherapy**	No	6644	263	1.0	0.024
	Yes	1153	117	0.7 (0.6–1.0)	
	Data missing	2	0		

Values in parentheses are 95% confidence intervals unless indicated otherwise; * values are numbers of nodes examined; ** Within 3 months of the primary operation.

similar to that previously reported [70 79 154 238 257 258] . The corresponding figure for the heterogeneous group of all patients with PC was 5.6 months (95% CI, 4.8 to 6.4), excluding 17 cases of PC diagnosed at autopsy. Five-year survival rates for these groups are presented in *Fig. 10*. However, to report the outcome related to treatment of PC was not a primary aim of this study. Nevertheless, there is increasing evidence today showing that in selected patients with PC, CRS and HIPEC improve survival.

In summary, colorectal PC was common in the present population-based study. Patients with colon cancer, particularly right-sided, advanced tumour and node status, and emergency and

non-radical procedures had an increased risk of developing metachronous PC. Defining risk factors may be important for early diagnosis and may help to select patients for aggressive treatment with curative intent.

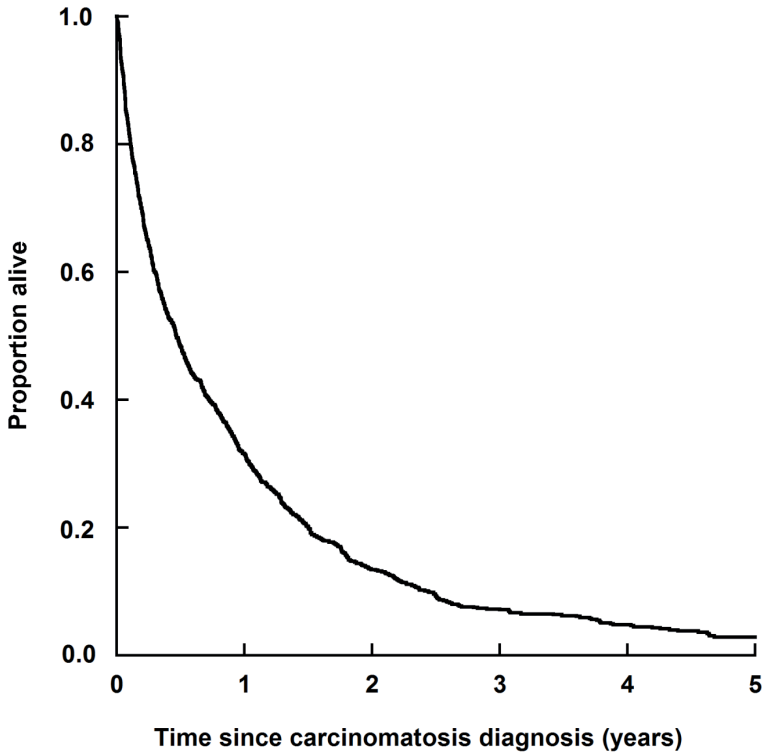


Figure 10a. *Five-year survival from the diagnosis of peritoneal carcinomatosis for all patients with peritoneal carcinomatosis.*

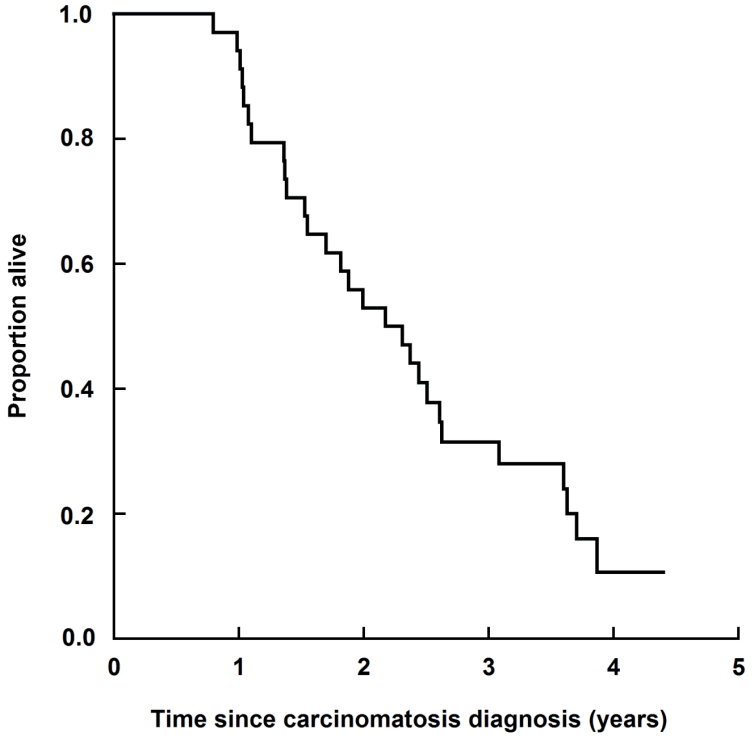


Figure 10b. *Five-year survival from diagnosis of peritoneal carcinomatosis in 34 patients treated with cytoreductive surgery and intraperitoneal chemotherapy.*

Paper III

Epidemiology and Prognosis of Ovarian Metastases from Colorectal Cancer

In all, 4566 women with colorectal cancer, without a previous history of gynaecological cancer, were included in the study cohort. Overall, synchronous and metachronous ovarian metastases were more common in women with colon cancer than in those with rectal cancer and were found in 69 of 3172 (2.2%) and 10 of 1394 (0.7%) respectively ($P < 0.001$). The prevalence of synchronous ovarian metastases at the time of diagnosis of the primary tumour was 0.9% (42 of 4566) for all colorectal cancer patients, 1.1 % (34 of 3172) among women with colon cancer, and 0.6% (8 of 1394) among those with rectal cancer ($P = 0.105$).
Metachronous ovarian metastases were found in 37 of 4527 (0.8%) of all colorectal cancer patients, or 35 of 3144 (1.1%) patients with colon cancer and two of 1383 (0.1%) with rectal cancer ($P<0.001$). Patients with colon cancer who developed ovarian metastases were younger, had a more advanced tumour stage and more often underwent emergency surgery for the primary tumour than those without a recurrent malignancy during follow-up. Survival in patients with ovarian metastases was poor.

Earlier single-centre studies report synchronous ovarian metastases in 0–9% of women with colorectal cancer and metachronous ovarian metastases in 0.9 –7% [93 101 127 209 274]. In the current study, asymptomtomatic ovarian metastases may be underdiagnosed for the same reasons as described for PC in paper II. Ovarian metastases were more common in patients with colon cancer than those with rectal cancer. One reason for this could be that carcinomatosis, with an increased risk of peritoneal spread to the ovaries, is more common in colon cancer patients than in rectal cancer patients [215]. Another contributing factor could be that nearly half of the women with rectal cancer were treated with radiotherapy. The effect of preoperative radiotherapy on the ovaries is unclear in women with rectal cancer. One possibility could be that radiotherapy itself eradicates micrometastases in the ovaries but also causes ovarian atrophy and impairs the ovarian blood supply, and thereby reduces the risk of haematogenous spread of the colorectal cancer to the ovaries.

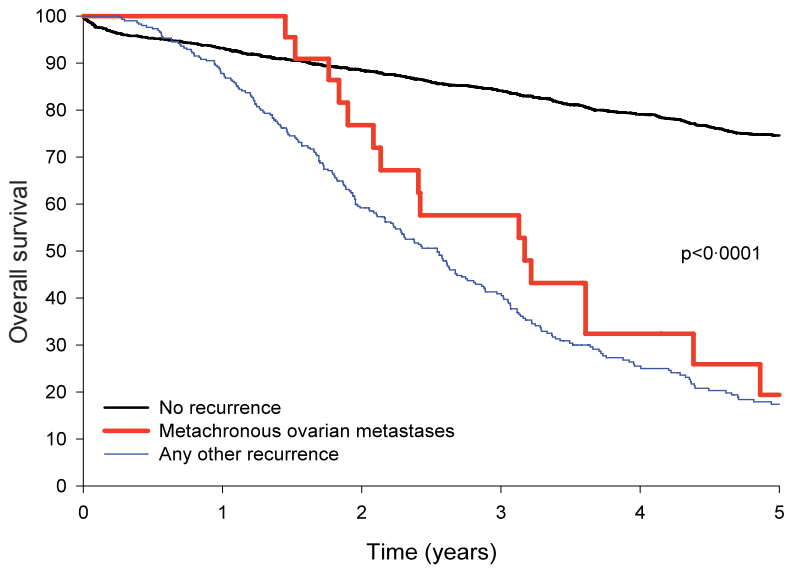
In total, unilateral oophorectomy was performed in 22 of 4566 (0.5%) and bilateral oophorectomy in 60 of 4566 (1%) women with colorectal cancer during the study period. Sixty-nine of these had ovarian metastases, three had direct overgrowth of the primary colorectal cancer, and ten had no pathology in the ovaries, but either distant metastases at other sites (n = 9) or a suspicion of ovarian involvement (n = 1).

Among patients with potentially cured colorectal cancer, e.g. patients with R0-resected colorectal cancer presenting with stage I–III disease, metachronous ovarian metastases were found in 22 of 1971 patients (1.1%) with colon cancer and one of 881 (0.1%) with rectal cancer ($P = 0.006$). The ovarian metastases were diagnosed after a median period of 16 (2–50) months from resection of the primary tumour. In colon cancer patients who developed metachronous ovarian metastases compared with those who did not, tumour stage was more advanced and emergency surgery was more common ($P < 0.001$). They were also younger ($P < 0.001$), which

may be a result of a decreasing risk of haematogenous tumour spread to atrophic ovaries in older women. This is in accord with other studies reporting an even lower median age in women developing ovarian metastases from colorectal cancer [49 127 147 198 240].

Survival in patients with ovarian metastases was poor. The estimated 5-year overall survival from diagnosis in all patients with synchronous ovarian metastases was 11 (CI 0.4–21) %. Other recent studies have reported a 25% 3-year survival and 27–44% 5-year survival in patients with synchronous ovarian metastases [49 80 127]. After complete resection of the malignant disease, reported 5-year disease-free and overall survival were 40% and 61%, respectively [80 127]. In the current study, survival of women with colon cancer who developed metachronous ovarian metastases was as poor as that of patients with other recurrences (*Fig. 11*).

In the discussion regarding prophylactic oophorectomy, it is of value to know the risk of developing metachronous ovarian metastases. In summary, this study shows that metachronous ovarian metastases from colorectal cancer are uncommon, and this does not favour routine prophylactic oophorectomy. More important factors to consider prior to surgery are the patient's age, individual risk of primary ovarian, breast and endometrial cancer, desire to preserve her hormone status and, not least, her own wishes.



Numbers at risk						
No recurrence	1654	1541	1279	1068	882	732
Metachronous ovarian metastases	22	22	16	12	6	3
Any other recurrence	295	259	164	103	56	35

Figure 11. *Overall survival after R0 resection of stage I–III colon cancer, grouped according to recurrence. P < 0.001 (log rank test)*

Paper IV

Potential Selection Bias in a Prospective Study on Sexual Function and Androgen Levels in Women with Rectal Cancer

The 82 women in the study cohort were younger than the 75 women who were eligible for inclusion but were not included (age 63 *vs* age 67, $P = 0.002$). There was a difference in the ASA classification, with lower comorbidity in the group of women who were included *vs* those who were not ($P = 0.025$). Clinical data and blood samples were obtained from all women in the study cohort. Serum levels of total testosterone (T) were above the detection limit in 76 women (92.7%). Fifty-seven women (69.5%) completed all the FSFI items. The proportion of women who had a partner was higher in this group compared with the women who did not complete all the FSFI items (49 out of 57 (86.0%) *vs* 7 out of 25 (28.0%) ($P < 0.001$).

Selection Bias

In total, treatment for rectal cancer was initiated in 237 women at the four study centres during the study period (*Fig. 12*). One hundred and fifty-seven of these women (66.2%) were eligible for inclusion in the study. In all, 82 of the 157 (52.2%) eligible women were included at the time of analysis. The reasons for not entering the study are shown in *Fig. 12*. Forty-two women were never invited to participate, thirty-two declined to join the study, and one was not included for unknown reasons.

Patients treated at the study centres might not be representative of the total population of female rectal cancer patients, which may reduce the external validity. Non-Swedish-speaking women were not included, and there may be demographic differences in, for example, educational level and socioeconomic or marital status between the study cohort and the total population of female rectal cancer patients. In addition, all four centres are high-volume ones with a high proportion of patients undergoing complete preoperative staging with pre- and post operative MDT assessments, which may influence treatment and outcome [6 215]. One of the centres is a referral centre for advanced tumours, which may explain the relatively high proportion of cT4 tumours (28% of patients eligible for inclusion). This can be compared with the 17% proportion of cT4 tumours in all Swedish patients undergoing abdominal resection of a rectal cancer stage I–IV 2010 [6].

An analysis of patient characteristics in all eligible women revealed a selection bias. Women in the study cohort were younger than the women who were not included (age 63 *vs* age 67, $P = 0.002$*)*. There was also a difference in the distribution of ASA classification, with a lower comorbidity in the group of women who were included *vs* those who were not ($P = 0.025$). The bias consists of both self-selection by declining to join and investigator-selection by not inviting to join. Over time, investigator-selection has decreased as a growing proportion of finally eligible women were invited to enter the study. A low inclusion rate has previously been reported in studies evaluating sexual function in women with rectal cancer [39 116 192]. Low response

rates to questionnaires or avoidance of specific items regarding sexual function is another important limitation, particularly in female patients [108 116 218 265]. Response rates of less than 50% are common. [30 96 108 218 242].In the present study, 57 women (69.5%) completed all nineteen FSFI items (complete FSFI responders) and 25 (30.5%) did not (incomplete FSFI responders). The proportion of women who had a partner was significantly higher in the group of complete FSFI responders than in those who were incomplete FSFI responders (49 of 57 (86.0%) *vs* 7 of 25 (28.0%) ($P < 0.001$)). The largest amount of missing or invalid data was found in two of the satisfaction items that cannot be adequately answered by sexually inactive individuals. These items concern satisfaction with the sexual relationship with the partner and overall sexual life, and there is no answer option such as "not relevant".

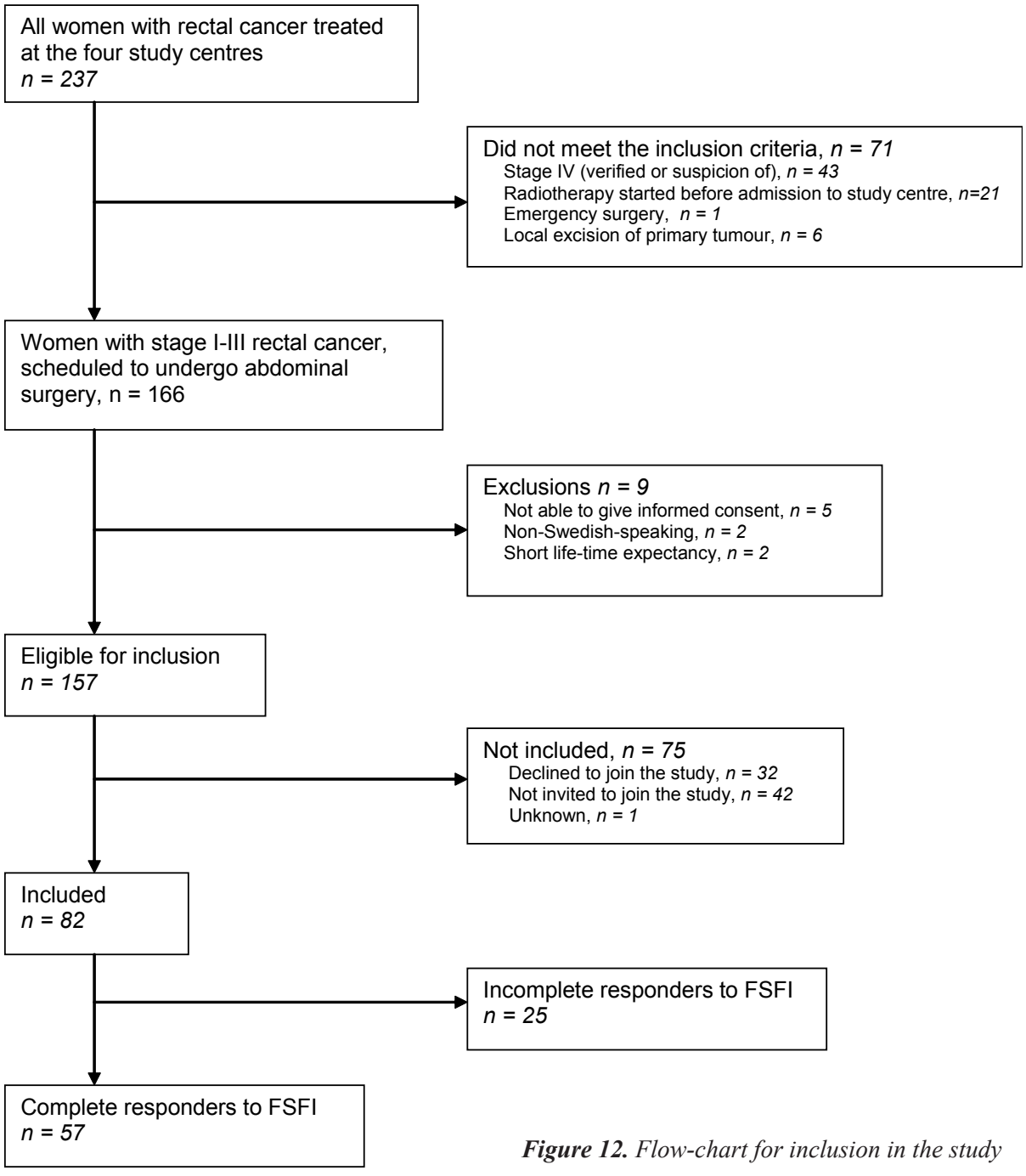


Figure 12. *Flow-chart for inclusion in the study*

As a consequence, mean and median total FSFI scores are representative for a subgroup of the cohort and may exclude women who have the poorest sexual function. The domain scores represent women who responded to the corresponding items in that specific domain and therefore better reflect the sexual function of the entire study cohort. Differences between included *vs* not included women reduce the external validity and differences between complete *vs* incomplete FSFI responders reduce the internal validity.

Feasibility

Feasibility was good. When the initial inclusion rate was slow, reminders at every MDT conference and regular updates of the number of patients included per centre were issued by e-mail. As a result, the proportion of women eligible for inclusion invited to join the study increased to nearly 100% during the study period at least in two of the centres (data not shown). Blood samples were drawn and clinical data obtained from all women in the study cohort. Compliance was high concerning FSFI data, with a total response frequency to all 19 FSFI items of 1459 of 1558 (93.6%). Incomplete FSFI responses appeared to be mainly an effect of questionnaire design. Seventy-six women (92.7%) had total T at or above the lowest level for detection, thus indicating active ovarian androgen production and adequate hormone measurements.

Information Bias

The FSFI assesses six aspects of female sexual function (desire, arousal, lubrication, orgasm, sexual satisfaction, and dyspareunia) [204]. Sexual activity is clearly defined as caressing, foreplay, masturbation, or vaginal intercourse, thus not excluding women without a partner. However, the FSFI is validated only for sexually active women, although it is used in studies including both women who are and who are not sexually active, which complicates the interpretation of data [58 108 116 148 165]. The FSFI provides a total score, ranging from 2 to 36. A high FSFI total score represents good sexual function, while a low score could signify dysfunction *and/or* sparse sexual activity. The absence of sexual activity resulting in low scores could be interpreted as a surrogate marker for sexual dysfunction. On the other hand, sexual inactivity may be a result of an individual's lack of desire or opportunity for sexual activity and may not be an accurate reflection of physiological functionality. This methodological limitation of FSFI has been discussed and suggestions for improvement have been published, but not yet implemented [29 84 166]. It is important to note that the FSFI total score cut-off for sexual dysfunction (26.5) has been established for sexually active women, using data from a group with a mean age of 36 years [262]. In the current study, 29 of the 41 sexually active complete responders (70.7%) had a total FSFI score of < 26.5, which indicates sexual dysfunction. Mean and median total FSFI scores for all the complete FSFI responders were 16.4 ± 10.6 (SD) and 15.1 (range 2–32.3), respectively.

To the best of our knowledge, there is no validated instrument for measuring sexual function in sexually inactive women. The frequently used EORTC QLQ–CR38 systematically excludes sexually inactive women [230]. In the updated CR29, one of two items on sexual function

concerns dyspareunia and cannot be answered by women not including vaginal intercourse in their sexual activities [261].

An additional possible source of information bias is recall bias. In our study the women are instructed to answer the questionnaires according to the situation before they experienced symptoms from the tumour. Patient delay is sometimes considerable for rectal cancer symptoms, which may influence baseline data. However, to minimize recall bias, the study design was prospective.

Power

We hypothesized that the mean total FSFI score at baseline would decrease by at least 20% after treatment. A sample size of 99 women will have an 80% power to detect a difference in means of 3.020 (20% impairment), assuming a standard deviation of differences of 10.58, using a paired t-test with a 0.05 two-sided significance level. When loss-to-follow-up is accounted for, the new estimated sample size is 130 women. The initially planned cohort size of 60–80 women would not be sufficient to confirm the hypothesis concerning the primary outcome. The decision has been taken to continue inclusion of patients, now aiming for 130 women.

In summary, feasibility and patient compliance was good. Internal and external validity may be hampered by bias, in particular selection bias. The effect of selection bias on external validity may decline with a growing proportion of eligible women invited to enter the study. According to a new power analysis, a larger sample size than initially planned for is needed. Inclusion continues.

Conclusions

- Patients with stage IV colon cancer were less often assessed by a multidisciplinary team (MDT) and less often had metastasis surgery than stage IV rectal cancer patients. The proportion of patients with stage IV colon and rectal cancer assessed by an MDT increased during the study period, as did the proportion who had surgery for the metastases. MDT assessment opens up the opportunity for more aggressive treatment with better outcomes.

- Peritoneal carcinomatosis (PC) from colorectal cancer was common. Independent predictors for metachronous PC were age > 70 years, colon cancer, advanced T stage, advanced N stage, emergency surgery and non-radical resection of the primary tumour. Defining risk factors for peritoneal carcinomatosis may be important for early diagnosis and may help to select patients for aggressive treatment with curative intent.

- Ovarian metastases from colorectal cancer were uncommon. This does not support routine prophylactic oophorectomy in women with colorectal cancer. Patients developing ovarian metastases were younger, had a more advanced tumour stage, and more often underwent emergency surgery than those without a recurrence. Survival in colorectal cancer patients with ovarian metastases was poor.

- Feasibility was good and patient compliance was high in the ongoing study on sexual function and androgen levels in women with rectal cancer. Internal and external validity may be limited by bias, in particular selection bias. The effect of selection bias on external validity may decrease with a growing proportion of eligible women invited to enter the study.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Kolorektalcancer – aspekter på multidisciplinärt omhändertagande, metastaserande sjukdom och sexuell funktion

Bakgrund

Årligen drabbas drygt 6000 svenskar av kolorektalcancer (cancer i tjocktarm och ändtarm). Hos ungefär var femte patient har cancern redan hunnit sprida sig till andra organ när den upptäcks. Hur många patienter som drabbas av metastaser (dottertumörer) i specifika organ, t ex äggstockar eller bukhinna, är mindre känt. Även kunskapen om riskfaktorer för metastaser i olika organ är begränsad.

Kirurgisk och onkologisk behandling av kolorektalcancer och metastaser har utvecklats och förbättrats avsevärt de senaste decennierna. Den primära behandlingen är operation, som ofta kombineras med onkologisk behandling. T ex ges ofta tilläggsbehandling med cellgift efter operation för koloncancer (tjocktarmscancer) eller strålbehandling mot primärtumören inför operation av rektalcancer (ändtarmscancer). Hos patienter med metastaser i andra organ kan cellgiftsbehandling förlänga överlevnaden och förbättra livskvaliteten. Hos ett mindre andel av patienterna med metastaserande sjukdom är det möjligt att utföra ett botande kirurgiskt ingrepp som innefattar både primärtumör och metastaser. Även i detta fall kombineras kirurgin ofta med onkologisk behandling.
Metastaskirurgi görs framför allt vid begränsad levermetastasering, som är den vanligaste metastaslokalisationen. Även vid metastaser t ex till lunga, bukhinna eller äggstockar kan botande kirurgi vara möjlig.
De ökade behandlingsmöjligheterna har medfört ett behov av att diskutera behandlingsalternativ för patienter med kolorektalcancer i s k multidisciplinära team, MDT. Det multidisciplinära teamet består av kirurger, onkologer, röntgenläkare, patologer och specialistsjuksköterskor. Huvudsyftet är att besluta om optimal behandling för varje enskild patient, men också att underlätta kommunikation mellan olika vårdgivare och koordination av behandlingen.

Målet med behandlingen är bot eller maximal överlevnad. I takt med att behandlingsresultaten förbättrats har andra värden som livskvalitet och bieffekter av cancer och cancerbehandling blivit allt viktigare. Sexuell funktion har betydelse för livskvaliteten. Många studier har visat att den sexuella funktionen försämras efter strålbehandling och operation av rektalcancer hos manliga patienter. Detta har även påvisats hos kvinnliga patienter, men det vetenskapliga underlaget är svagare.

Bidragande orsaker till sexuell dysfunktion hos kvinnor och män som behandlats för rektalcancer kan vara effekter av det kirurgiska traumat, men också en minskad produktion av androgener (könshormoner). Hos kvinnor i alla åldrar produceras androgener i binjurebarken och

i äggstockarna. En möjlig biverkan av strålbehandling vid rektalcancer skulle kunna vara en minskad androgenproduktion i äggstockarna, men hittills har inga studier om detta publicerats. Androgenbrist hos kvinnor är bl a associerat med nedsatt sexuell funktion och psykologiskt välbefinnande.

Metoder och resultat

Delarbete I-III är stora s k populationsbaserade kohortstudier, som baseras på alla patienter med kolorektalcancer i Stockholmsregionen under en definierad tidperiod. Styrkan med populationsbaserade studier är att kohorten representeras av alla patienter i en geografiskt väldefinierad källpopulation (alla invånare i Stockholms Läns Landsting). Därmed undviks selektionsbias. Selektionsbias innebär att gruppen av studerade patienter skulle utgöras av en specifik, utvald grupp patienter som särskiljer sig från hela gruppen av kolorektalcancerpatienter. När selektionsbias minimeras ökar studiens generaliserbarhet, vilket innebär att resultaten från studien kan anses gälla för kolorektalcancerpatienter i allmänhet.

I delarbete I studeras i vilken utsträckning patienter med fjärrmetastaser bedöms av det multidisciplinära teamet, samt effekten av detta. Såväl MDT-bedömning som kirurgi av metastaser var vanligare vid rektalcancer än vid koloncancer, och andelen patienter som bedömdes multidisciplinärt ökade över tid. Den utvalda minoriteten patienter som bedömdes lämpliga för och genomgick metastaskirurgi hade en avsevärt längre överlevnad jämfört de patienter som inte genomgick metastaskirurgi.

Delarbete II visar att metastasering till bukhinnan, peritoneal karcinos, är vanligt. Riskfaktorer för peritoneal carcinos var koloncancer, avancerat stadium avseende primärtumör och lymfkörtlar, få undersökta lymfkörtlar, akutkirurgi och en icke-radikal resektion av primärtumören. Patienter över 70 år hade en minskad risk för peritoneal karcinos.

Delarbete III visar att metastaser till äggstockar, ovarialmetastaser, är ovanligt, ff a vid rektalcancer. Patienter som drabbades av ovarialmetastaser var yngre, hade ett mer avancerat tumörstadium och genomgick oftare akutkirurgi jämfört de som inte hade ovarialmetastaser. Överlevnaden hos patienter med ovarialmetastaser var kort.

Delarbete IV utvärderar genomförbarhet, generaliserbarhet och selektionsbias i en pågående studie om sexuell funktion och hormonnivåer hos kvinnor som behandlas för rektalcancer. Något förenklat mäts sexuell funktion (med frågeformulär) och hormonnivåer (med analys av blodprov) hos kvinnorna i studien före behandling och ett år efter behandling. Inför studiestart beräknades att en studiekohort på 60-80 kvinnor skulle vara tillräcklig för att påvisa den hypotetiska försämringen i sexuell funktion efter behandlingen.
I delarbete IV analyseras data från alla potentiellt inkluderbara patienter. Jämförelse av data från de 82 dittills inkluderade kvinnorna (studiekohorten) med de som inte inkluderades visar selektionbias. Patienterna i studiekohorten var något yngre och hade tidigare tumörstadium jämfört de som inte inkluderades. Dock har studiekohorten som grupp ett avancerat tumörsta-

dium vid en nationell jämförelse. Det kan förklaras av att ett av de fyra sjukhusen som är med i studien är ett centrum för avancerad rektalcancerkirurgi, vilket avspeglas i patientklientelet.
Följsamheten hos patienterna i studiekohorten var hög. Alla lämnade blodprov, och majoriteten av frågorna i frågeformuläret besvarades. Att ha en partner och vara sexuellt aktiv var vanligare hos de patienter som besvarade alla frågorna jämfört de som inte gjorde det. Frågorna som oftast lämnades obesvarade är ställda på ett sådant sätt att de saknar relevans för den som inte har ett aktivt sexliv med en partner.
Baserat på enkätdata före behandling gjordes en ny analys avseende hur stort antal patienter som krävs för att bekräfta hypotesen. Analysen visade att patientgruppen skulle behöva vara större än tidigare beräknat.

Konklusion

Sammanfattningsvis visar avhandlingen att en ökande andel patienter med metastaserande kolorektalcancer bedömdes på MDT-konferens och genomgick metastaskirurgi.
Förekomsten av och riskfaktorer för peritoneal carcinos och ovarialmetastaser definierades, vilket kan underlätta beslut om behandling och uppföljning.
Analys av data från studien om sexuell funktion och hormonnivåer hos kvinnor med rektalcancer visar god genomförbarhet men viss selektionsbias. Inklusionen av patienter i studien fortsätter.

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References

1. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet 2001;358(9290):1291-304.
2. *Colorectal cancer: National Clinical Guidelines 2008*. http://www.vinkcancer.se/Global/RCCUppsalaOrebro/V%c3%a5rdprocesser/kolorektal/v%c3%a5rdprogram/nat_vardprogram_08_omvvp_110412.pdf. 2008.
3. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997;336(14):980-7.
4. The role of testosterone therapy in postmenopausal women: position statement of The North American Menopause Society. Menopause 2005;12(5):496-511; quiz 649.
5. S*wedish Colon Cancer Registry*http://www.vinkcancer.se/Global/Diagnoser/kolorektal/rapporter/colon2010_110927.pdf. 2010.
6. *Swedish Rectal Cancer Registry.* http://www.vinkcancer.se/Global/Diagnoser/kolorektal/rapporter/rekti2010b.pdf. 2010.
7. Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 1999;81(2):214-8.
8. Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006;13(10):1271-80.
9. Adam R. Developing strategies for liver metastases from colorectal cancer. Semin Oncol 2007;34(2 Suppl 1):S7-11.
10. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240(4):644-57; discussion 57-8.
11. Ala-Fossi SL, Maenpaa J, Aine R, Punnonen R. Ovarian testosterone secretion during perimenopause. Maturitas 1998;29(3):239-45.
12. Alexander GM, Sherwin BB. Sex steroids, sexual behavior, and selection attention for erotic stimuli in women using oral contraceptives. Psychoneuroendocrinology 1993;18(2):91-102.
13. Allegra CJ, Yothers G, O'Connell MJ, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol 2011;29(1):11-6.
14. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27(19):3109-16.
15. Antoch G, Saoudi N, Kuehl H, et al. Accuracy of whole-body dual-modality fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET. J Clin Oncol 2004;22(21):4357-68.
16. Arndt V, Merx H, Stegmaier C, Ziegler H, Brenner H. Restrictions in quality of life in colorectal cancer patients over three years after diagnosis: a population based study. Eur J Cancer 2006;42(12):1848-57.
17. Augestad KM, Lindsetmo RO, Stulberg J, et al. International preoperative rectal cancer management: staging, neoadjuvant treatment, and impact of multidisciplinary teams. World J Surg 2010;34(11):2689-700.
18. Bachmann G, Bancroft J, Braunstein G, et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. Fertil Steril 2002;77(4):660-5.
19. Bachmann GA, Leiblum SR. Sexuality in sexagenarian women. Maturitas 1991;13(1):43-50.
20. Banerjee S, Kapur S, Moran BJ. The role of prophylactic oophorectomy in women undergoing surgery for colorectal cancer. Colorectal Dis 2005;7(3):214-7.

21. Barlogie B, Corry PM, Drewinko B. In vitro thermochemotherapy of human colon cancer cells with cis-dichlorodiammineplatinum(II) and mitomycin C. Cancer Res 1980;40(4):1165-8.
22. Bauer JJ, Gelernt IM, Salky B, Kreel I. Sexual dysfunction following proctocolectomy for benign disease of the colon and rectum. Ann Surg 1983;197(3):363-7.
23. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. N Engl J Med 1999;340(18):1383-9.
24. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Occurrence of second cancers in patients treated with radiotherapy for rectal cancer. J Clin Oncol 2005;23(25):6126-31.
25. Birnkrant A, Sampson J, Sugarbaker PH. Ovarian metastasis from colorectal cancer. Dis Colon Rectum 1986;29(11):767-71.
26. Blodgett TM, Meltzer CC, Townsend DW. PET/CT: form and function. Radiology 2007;242(2):360-85.
27. Blomqvist L, Glimelius B. The 'good', the 'bad', and the 'ugly' rectal cancers. Acta Oncol 2008;47(1):5-8.
28. Bloom JR, Petersen DM, Kang SH. Multi-dimensional quality of life among long-term (5+ years) adult cancer survivors. Psychooncology 2007;16(8):691-706.
29. Boehmer U, Timm A, Ozonoff A, Potter J. Applying the Female Sexual Functioning Index to Sexual Minority Women. J Womens Health (Larchmt) 2011.
30. Bohm G, Kirschner-Hermanns R, Decius A, Heussen N, Schumpelick V, Willis S. Anorectal, bladder, and sexual function in females following colorectal surgery for carcinoma. Int J Colorectal Dis 2008;23(9):893-900.
31. Bosetti C, Bravi F, Negri E, La Vecchia C. Oral contraceptives and colorectal cancer risk: a systematic review and meta-analysis. Hum Reprod Update 2009;15(5):489-98.
32. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355(11):1114-23.
33. Bouvier AM, Bauvin E, Danzon A, et al. Place of multidisciplinary consulting meetings and clinical trials in the management of colorectal cancer in France in 2000. Gastroenterol Clin Biol 2007;31(3):286-91.
34. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 2008;26(22):3687-94.
35. Braunstein GD. The Endocrine Society Clinical Practice Guideline and The North American Menopause Society position statement on androgen therapy in women: another one of Yogi's forks. J Clin Endocrinol Metab 2007;92(11):4091-3.
36. Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Arch Intern Med 2005;165(14):1582-9.
37. Brenner H, Bouvier AM, Foschi R, et al. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: The EUROCARE study. Int J Cancer 2011.
38. Bruheim K, Svartberg J, Carlsen E, et al. Radiotherapy for rectal cancer is associated with reduced serum testosterone and increased FSH and LH. Int J Radiat Oncol Biol Phys 2008;70(3):722-7.
39. Bruheim K, Tveit KM, Skovlund E, et al. Sexual function in females after radiotherapy for rectal cancer. Acta Oncol 2010;49(6):826-32.
40. Buchli C, Martling A, Arver S, Holm T. Testicular Function after Radiotherapy for Rectal Cancer-A Review. J Sex Med 2011.
41. Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials. Ann Oncol 2010;21(9):1743-50.
42. Burger HG, Dudley EC, Cui J, Dennerstein L, Hopper JL. A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin levels through the menopause transition. J Clin Endocrinol Metab 2000;85(8):2832-8.

43. Burton S, Brown G, Daniels IR, Norman AR, Mason B, Cunningham D. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? Br J Cancer 2006;94(3):351-7.
44. Buunen M, Veldkamp R, Hop WC, et al. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. Lancet Oncol 2009;10(1):44-52.
45. Camma C, Giunta M, Fiorica F, Pagliaro L, Craxi A, Cottone M. Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. Jama 2000;284(8):1008-15.
46. Cashin PH, Graf W, Nygren P, Mahteme H. Intraoperative hyperthermic versus postoperative normothermic intraperitoneal chemotherapy for colonic peritoneal carcinomatosis: a case-control study. Ann Oncol 2011.
47. Cedermark B, Johansson H, Rutqvist LE, Wilking N. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Colorectal Cancer Study Group. Cancer 1995;75(9):2269-75.
48. Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. Cancer 1989;63(2):364-7.
49. Chung TS, Chang HJ, Jung KH, et al. Role of surgery in the treatment of ovarian metastases from colorectal cancer. J Surg Oncol 2009;100(7):570-4.
50. ClinicalTrials.gov. *Trial Comparing Simple Follow-up to Exploratory Laparotomy Plus "in Principle" (Hyperthermic Intraperitoneal Chemotherapy) HIPEC in Colorectal Patients (ProphyloCHIP)*. http://clinicaltrials.gov/ct2/show/NCT01226394.
51. Coenen CM, Thomas CM, Borm GF, Hollanders JM, Rolland R. Changes in androgens during treatment with four low-dose contraceptives. Contraception 1996;53(3):171-6.
52. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. Menopause and the risk of coronary heart disease in women. N Engl J Med 1987;316(18):1105-10.
53. Cook AD, Single R, McCahill LE. Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: an analysis of surveillance, epidemiology, and end results data, 1988 to 2000. Ann Surg Oncol 2005;12(8):637-45.
54. Crilly RG, Francis RM, Nordin BE. Steroid hormones, ageing and bone. Clin Endocrinol Metab 1981;10(1):115-39.
55. Cummings LC, Payes JD, Cooper GS. Survival after hepatic resection in metastatic colorectal cancer: a population-based study. Cancer 2007;109(4):718-26.
56. Cummings SR, Browner WS, Bauer D, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group. N Engl J Med 1998;339(11):733-8.
57. Cunningham D, Atkin W, Lenz HJ, et al. Colorectal cancer. Lancet 2010;375(9719):1030-47.
58. da Silva GM, Hull T, Roberts PL, et al. The effect of colorectal surgery in female sexual function, body image, self-esteem and general health: a prospective study. Ann Surg 2008;248(2):266-72.
59. Davis S, Papalia MA, Norman RJ, et al. Safety and efficacy of a testosterone metered-dose transdermal spray for treating decreased sexual satisfaction in premenopausal women: a randomized trial. Ann Intern Med 2008;148(8):569-77.
60. Davis SR, Davison SL, Donath S, Bell RJ. Circulating androgen levels and self-reported sexual function in women. Jama 2005;294(1):91-6.
61. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab 2005;90(7):3847-53.
62. Davison SL, Bell RJ, LaChina M, Holden SL, Davis SR. Sexual function in well women: stratification by sexual satisfaction, hormone use, and menopause status. J Sex Med 2008;5(5):1214-22.
63. Dedrick RL. Theoretical and experimental bases of intraperitoneal chemotherapy. Semin Oncol 1985;12(3 Suppl 4):1-6.
64. Dedrick RL, Myers CE, Bungay PM, DeVita VT, Jr. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep 1978;62(1):1-11.

65. Delellis Henderson K, Duan L, Sullivan-Halley J, et al. Menopausal hormone therapy use and risk of invasive colon cancer: the California Teachers Study. Am J Epidemiol;171(4):415-25.
66. Deliganis AV, Maravilla KR, Heiman JR, et al. Female genitalia: dynamic MR imaging with use of MS-325 initial experiences evaluating female sexual response. Radiology 2002;225(3):791-9.
67. Dennerstein L, Burrows GD, Wood C, Hyman G. Hormones and sexuality: effect of estrogen and progestogen. Obstet Gynecol 1980;56(3):316-22.
68. Dennerstein L, Lehert P, Burger H. The relative effects of hormones and relationship factors on sexual function of women through the natural menopausal transition. Fertil Steril 2005;84(1):174-80.
69. Dukes C. The classification of cancer of the rectum. J of Path and Bact 1932;35:323-32.
70. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010;28(1):63-8.
71. Elias D, Goere D, Di Pietrantonio D, et al. Results of systematic second-look surgery in patients at high risk of developing colorectal peritoneal carcinomatosis. Ann Surg 2008;247(3):445-50.
72. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol 2009;27(5):681-5.
73. Engstrom PF, Arnoletti JP, Benson AB, 3rd, et al. NCCN Clinical Practice Guidelines in Oncology: colon cancer. J Natl Compr Canc Netw 2009;7(8):778-831.
74. Evers DJ, Verwaal VJ. Indication for oophorectomy during cytoreduction for intraperitoneal metastatic spread of colorectal or appendiceal origin. Br J Surg 2010;98(2):287-92.
75. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer;127(12):2893-917.
76. Floter A. Testosterone Treatment in Women - An Overview. Curr Wom Health Rew 2009;5:29-43.
77. Floter A, Nathorst-Boos J, Carlstrom K, von Schoultz B. Addition of testosterone to estrogen replacement therapy in oophorectomized women: effects on sexuality and well-being. Climacteric 2002;5(4):357-65.
78. Flöter A. Testosterone treatment in women - an overview. Curr Women's Health Rev 2009;5:29-43.
79. Franko J, Ibrahim Z, Gusani NJ, Holtzman MP, Bartlett DL, Zeh HJ, 3rd. Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. Cancer 2010;116(16):3756-62.
80. Fujiwara A, Noura S, Ohue M, et al. Significance of the resection of ovarian metastasis from colorectal cancers. J Surg Oncol 2010;102(6):582-7.
81. Gallagher DJ, Kemeny N. Metastatic colorectal cancer: from improved survival to potential cure. Oncology 2010;78(3-4):237-48.
82. Garofalo A, Valle M. Laparoscopy in the management of peritoneal carcinomatosis. Cancer J 2009;15(3):190-5.
83. Genazzani AR, Monteleone P, Gambacciani M. Hormonal influence on the central nervous system. Maturitas 2002;43 Suppl 1:S11-7.
84. Gerstenberger EP, Rosen RC, Brewer JV, et al. Sexual desire and the female sexual function index (FSFI): a sexual desire cutpoint for clinical interpretation of the FSFI in women with and without hypoactive sexual desire disorder. J Sex Med 2010;7(9):3096-103.
85. Gillessen S, Templeton A, Marra G, Kuo YF, Valtorta E, Shahinian VB. Risk of colorectal cancer in men on long-term androgen deprivation therapy for prostate cancer. J Natl Cancer Inst 2010;102(23):1760-70.
86. Giraldi A, Rellini A, Pfaus JG, et al. Questionnaires for assessment of female sexual dysfunction: a review and proposal for a standardized screener. J Sex Med 2011;8(10):2681-706.

87. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol 2004;22(16):3284-92.
88. Glehen O, Osinsky D, Cotte E, et al. Intraperitoneal chemohyperthermia using a closed abdominal procedure and cytoreductive surgery for the treatment of peritoneal carcinomatosis: morbidity and mortality analysis of 216 consecutive procedures. Ann Surg Oncol 2003;10(8):863-9.
89. Glimelius B, Beets-Tan R, Blomqvist L, et al. Mesorectal fascia instead of circumferential resection margin in preoperative staging of rectal cancer. J Clin Oncol 2011;29(16):2142-3.
90. Glimelius B, Holm T, Blomqvist L. Chemotherapy in addition to preoperative radiotherapy in locally advanced rectal cancer - a systematic overview. Rev Recent Clin Trials 2008;3(3):204-11.
91. Gonzalez-Moreno S, Kusamura S, Baratti D, Deraco M. Postoperative residual disease evaluation in the locoregional treatment of peritoneal surface malignancy. J Surg Oncol 2008;98(4):237-41.
92. Gracia CR, Sammel MD, Freeman EW, Liu L, Hollander L, Nelson DB. Predictors of decreased libido in women during the late reproductive years. Menopause 2004;11(2):144-50.
93. Graffner HO, Alm PO, Oscarson JE. Prophylactic oophorectomy in colorectal carcinoma. Am J Surg 1983;146(2):233-5.
94. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. Am J Med 1999;106(5):574-82.
95. Guay A, Munarriz R, Jacobson J, et al. Serum androgen levels in healthy premenopausal women with and without sexual dysfunction: Part A. Serum androgen levels in women aged 20-49 years with no complaints of sexual dysfunction. Int J Impot Res 2004;16(2):112-20.
96. Guren MG, Eriksen MT, Wiig JN, et al. Quality of life and functional outcome following anterior or abdominoperineal resection for rectal cancer. Eur J Surg Oncol 2005;31(7):735-42.
97. Guyot F, Faivre J, Manfredi S, Meny B, Bonithon-Kopp C, Bouvier AM. Time trends in the treatment and survival of recurrences from colorectal cancer. Ann Oncol 2005;16(5):756-61.
98. Hallbook O, Pahlman L, Krog M, Wexner SD, Sjodahl R. Randomized comparison of straight and colonic J pouch anastomosis after low anterior resection. Ann Surg 1996;224(1):58-65.
99. Hallbook O, Sjodahl R. Comparison between the colonic J pouch-anal anastomosis and healthy rectum: clinical and physiological function. Br J Surg 1997;84(10):1437-41.
100. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol 2011;29(11):1465-71.
101. Hanna NN, Cohen AM. Ovarian neoplasms in patients with colorectal cancer: understanding the role of prophylactic oophorectomy. Clin Colorectal Cancer 2004;3(4):215-22.
102. Harris GJ, Church JM, Senagore AJ, et al. Factors affecting local recurrence of colonic adenocarcinoma. Dis Colon Rectum 2002;45(8):1029-34.
103. Hassan I, Cima RR. Quality of life after rectal resection and multimodality therapy. J Surg Oncol 2007;96(8):684-92.
104. Havenga K, Maas CP, DeRuiter MC, Welvaart K, Trimbos JB. Avoiding long-term disturbance to bladder and sexual function in pelvic surgery, particularly with rectal cancer. Semin Surg Oncol 2000;18(3):235-43.
105. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg 1982;69(10):613-6.
106. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986;1(8496):1479-82.

107. Hein PA, Kremser C, Judmaier W, et al. Diffusion-weighted magnetic resonance imaging for monitoring diffusion changes in rectal carcinoma during combined, preoperative chemoradiation: preliminary results of a prospective study. Eur J Radiol 2003;45(3):214-22.
108. Hendren SK, O'Connor BI, Liu M, et al. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. Ann Surg 2005;242(2):212-23.
109. Hermanek P, Wiebelt H, Staimmer D, Riedl S. Prognostic factors of rectum carcinoma--experience of the German Multicentre Study SGCRC. German Study Group Colo-Rectal Carcinoma. Tumori 1995;81(3 Suppl):60-4.
110. Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. Colorectal Dis 2009;11(4):354-64; discussion 64-5.
111. Hong NJ, Wright FC, Gagliardi AR, Paszat LF. Examining the potential relationship between multidisciplinary cancer care and patient survival: an international literature review. J Surg Oncol 2010;102(2):125-34.
112. Iitsuka Y, Kaneshima S, Tanida O, Takeuchi T, Koga S. Intraperitoneal free cancer cells and their viability in gastric cancer. Cancer 1979;44(4):1476-80.
113. Inskip PD, Eby NL, Cookfair D, et al. Serum estrogen and androgen levels following treatment for cervical cancer. Cancer Epidemiol Biomarkers Prev 1994;3(1):37-45.
114. Jacquet P, Averbach A, Stuart OA, Chang D, Sugarbaker PH. Hyperthermic intraperitoneal doxorubicin: pharmacokinetics, metabolism, and tissue distribution in a rat model. Cancer Chemother Pharmacol 1998;41(2):147-54.
115. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology 2010;138(6):2044-58.
116. Jayne DG, Brown JM, Thorpe H, Walker J, Quirke P, Guillou PJ. Bladder and sexual function following resection for rectal cancer in a randomized clinical trial of laparoscopic versus open technique. Br J Surg 2005;92(9):1124-32.
117. Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. Br J Surg 2002;89(12):1545-50.
118. Jayne DG, Thorpe HC, Copeland J, Quirke P, Brown JM, Guillou PJ. Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. Br J Surg 2010;97(11):1638-45.
119. Jones RB, Myers CE, Guarino AM, Dedrick RL, Hubbard SM, DeVita VT. High volume intraperitoneal chemotherapy ("belly bath") for ovarian cancer. Pharmacologic basis and early results. Cancer Chemother Pharmacol 1978;1(3):161-6.
120. Kampinga HH. Cell biological effects of hyperthermia alone or combined with radiation or drugs: a short introduction to newcomers in the field. Int J Hyperthermia 2006;22(3):191-6.
121. Kanemitsu Y, Hirai T, Komori K, Kato T. Survival benefit of high ligation of the inferior mesenteric artery in sigmoid colon or rectal cancer surgery. Br J Surg 2006;93(5):609-15.
122. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345(9):638-46.
123. Karantanas AH, Yarmenitis S, Papanikolaou N, Gourtsoyiannis N. Preoperative imaging staging of rectal cancer. Dig Dis 2007;25(1):20-32.
124. Kauff ND, Barakat RR. Risk-reducing salpingo-oophorectomy in patients with germline mutations in BRCA1 or BRCA2. J Clin Oncol 2007;25(20):2921-7.
125. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346(21):1609-15.
126. Kendal WS, Nicholas G. A population-based analysis of second primary cancers after irradiation for rectal cancer. Am J Clin Oncol 2007;30(4):333-9.
127. Kim DD, Park IJ, Kim HC, Yu CS, Kim JC. Ovarian metastases from colorectal cancer: a clinicopathological analysis of 103 patients. Colorectal Dis 2009;11(1):32-8.
128. Kitajima K, Suzuki K, Senda M, et al. FDG PET/CT features of ovarian metastasis. Clin Radiol 2010;66(3):264-8.
129. Koornstra JJ, Mourits MJ, Sijmons RH, Leliveld AM, Hollema H, Kleibeuker JH. Management of extracolonic tumours in patients with Lynch syndrome. Lancet Oncol 2009;10(4):400-8.

130. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 2009;27(22):3677-83.
131. Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. Ann Surg 2006;243(2):212-22.
132. Koyama T, Mikami Y, Saga T, Tamai K, Togashi K. Secondary ovarian tumors: spectrum of CT and MR features with pathologic correlation. Abdom Imaging 2007.
133. Kukkonen TM, Binik YM, Amsel R, Carrier S. Thermography as a physiological measure of sexual arousal in both men and women. J Sex Med 2007;4(1):93-105.
134. Kusamura S, Younan R, Baratti D, et al. Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion: analysis of morbidity and mortality in 209 peritoneal surface malignancies treated with closed abdomen technique. Cancer 2006;106(5):1144-53.
135. Kusumoto T, Holden SA, Ara G, Teicher BA. Hyperthermia and platinum complexes: time between treatments and synergy in vitro and in vivo. Int J Hyperthermia 1995;11(4):575-86.
136. Laan E, van Driel EM, van Lunsen RH. Genital responsiveness in healthy women with and without sexual arousal disorder. J Sex Med 2008;5(6):1424-35.
137. Laan E, van Lunsen RH, Everaerd W. The effects of tibolone on vaginal blood flow, sexual desire and arousability in postmenopausal women. Climacteric 2001;4(1):28-41.
138. Labianca R, Nordlinger B, Beretta GD, Brouquet A, Cervantes A. Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v70-7.
139. Lahaye MJ, Engelen SM, Nelemans PJ, et al. Imaging for predicting the risk factors--the circumferential resection margin and nodal disease--of local recurrence in rectal cancer: a meta-analysis. Semin Ultrasound CT MR 2005;26(4):259-68.
140. Lamb BW, Brown KF, Nagpal K, Vincent C, Green JS, Sevdalis N. Quality of care management decisions by multidisciplinary cancer teams: a systematic review. Ann Surg Oncol 2011;18(8):2116-25.
141. Lambregts DM, Vandecaveye V, Barbaro B, et al. Diffusion-weighted MRI for selection of complete responders after chemoradiation for locally advanced rectal cancer: a multicenter study. Ann Surg Oncol;18(8):2224-31.
142. Lange MM, Marijnen CA, Maas CP, et al. Risk factors for sexual dysfunction after rectal cancer treatment. Eur J Cancer 2009;45(9):1578-88.
143. Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, von Muhlen D. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. J Clin Endocrinol Metab 2000;85(2):645-51.
144. Lee SJ, Lee J, Lim HY, et al. Survival benefit from ovarian metastatectomy in colorectal cancer patients with ovarian metastasis: a retrospective analysis. Cancer Chemother Pharmacol 2009;66(2):229-35.
145. Lefevre JH, Elias DM. Cytoreductive surgery plus intraperitoneal chemohyperthermia in patients with colorectal cancer at high risk for local-regional recurrence. Cancer J 2009;15(3):200-3.
146. Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg 2006;93(4):465-74.
147. Lewis MR, Deavers MT, Silva EG, Malpica A. Ovarian involvement by metastatic colorectal adenocarcinoma: still a diagnostic challenge. Am J Surg Pathol 2006;30(2):177-84.
148. Liang JT, Lai HS, Lee PH, Chang KJ. Laparoscopic pelvic autonomic nerve-preserving surgery for sigmoid colon cancer. Ann Surg Oncol 2008;15(6):1609-16.
149. Lordan JT, Karanjia ND, Quiney N, Fawcett WJ, Worthington TR. A 10-year study of outcome following hepatic resection for colorectal liver metastases - the effect of evaluation in a multidisciplinary team setting. Eur J Surg Oncol 2008.
150. MacDermid E, Hooton G, MacDonald M, et al. Improving patient survival with the colorectal cancer multi-disciplinary team. Colorectal Dis 2009;11(3):291-5.

151. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet 1993;341(8843):457-60.
152. Machado M, Nygren J, Goldman S, Ljungqvist O. Similar outcome after colonic pouch and side-to-end anastomosis in low anterior resection for rectal cancer: a prospective randomized trial. Ann Surg 2003;238(2):214-20.
153. Maggiori L, Elias D. Curative treatment of colorectal peritoneal carcinomatosis: current status and future trends. Eur J Surg Oncol 2010;36(7):599-603.
154. Mahteme H, Hansson J, Berglund A, et al. Improved survival in patients with peritoneal metastases from colorectal cancer: a preliminary study. Br J Cancer 2004;90(2):403-7.
155. Mamounas E, Wieand S, Wolmark N, et al. Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B versus Dukes' C colon cancer: results from four National Surgical Adjuvant Breast and Bowel Project adjuvant studies (C-01, C-02, C-03, and C-04). J Clin Oncol 1999;17(5):1349-55.
156. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 2006;244(2):254-9.
157. Marijnen CA, Kapiteijn E, van de Velde CJ, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2002;20(3):817-25.
158. Marijnen CA, van de Velde CJ, Putter H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2005;23(9):1847-58.
159. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. Cancer 2001;92(4):896-902.
160. Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. Lancet 2000;356(9224):93-6.
161. Matthiessen P, Hallbook O, Rutegard J, Simert G, Sjodahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007;246(2):207-14.
162. McCormick CC, Giuntoli RL, 2nd, Gardner GJ, et al. The role of cytoreductive surgery for colon cancer metastatic to the ovary. Gynecol Oncol 2007;105(3):791-5.
163. McEwen BS, Davis PG, Jellinck PH, et al. Steroid hormone receptors, brain cell function, and the neuroendocrine system. Adv Biochem Psychopharmacol 1980;21:383-90.
164. Melton LJ, 3rd, Khosla S, Malkasian GD, Achenbach SJ, Oberg AL, Riggs BL. Fracture risk after bilateral oophorectomy in elderly women. J Bone Miner Res 2003;18(5):900-5.
165. Meston CM. Validation of the Female Sexual Function Index (FSFI) in women with female orgasmic disorder and in women with hypoactive sexual desire disorder. J Sex Marital Ther 2003;29(1):39-46.
166. Meyer-Bahlburg HF, Dolezal C. The female sexual function index: a methodological critique and suggestions for improvement. J Sex Marital Ther 2007;33(3):217-24.
167. Mitchard JR, Love SB, Baxter KJ, Shepherd NA. How important is peritoneal involvement in rectal cancer? A prospective study of 331 cases. Histopathology;57(5):671-9.
168. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990;322(6):352-8.
169. Mohamed F, Cecil T, Moran B, Sugarbaker P. A new standard of care for the management of peritoneal surface malignancy. Curr Oncol 2011;18(2):e84-96.
170. Mohamed F, Marchettini P, Stuart OA, Urano M, Sugarbaker PH. Thermal enhancement of new chemotherapeutic agents at moderate hyperthermia. Ann Surg Oncol 2003;10(4):463-8.

171. Moosmann N, von Weikersthal LF, Vehling-Kaiser U, et al. Cetuximab plus capecitabine and irinotecan compared with cetuximab plus capecitabine and oxaliplatin as first-line treatment for patients with metastatic colorectal cancer: AIO KRK-0104--a randomized trial of the German AIO CRC study group. J Clin Oncol 2011;29(8):1050-8.
172. Moran BJ. Decision-making and technical factors account for the learning curve in complex surgery. J Public Health (Oxf) 2006;28(4):375-8.
173. Morris E, Forman D, Haward B. The impact of the Calman-Hine report: analysis of breast and colorectal cancer surgical workloads and the degree of surgical site specialization in the Yorkshire region of the UK, 1990-2000. Eur J Cancer Care (Engl) 2007;16(2):150-5.
174. Morrow M, Enker WE. Late ovarian metastases in carcinoma of the colon and rectum. Arch Surg 1984;119(12):1385-8.
175. Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. Am J Surg Pathol 2002;26(3):350-7.
176. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol 2008;26(2):303-12.
177. Nathorst-Boos J, Wiklund I, Mattsson LA, Sandin K, von Schoultz B. Is sexual life influenced by transdermal estrogen therapy? A double blind placebo controlled study in postmenopausal women. Acta Obstet Gynecol Scand 1993;72(8):656-60.
178. Otchy D, Hyman NH, Simmang C, et al. Practice parameters for colon cancer. Dis Colon Rectum 2004;47(8):1269-84.
179. Oussoultzoglou E, Bachellier P, Rosso E, et al. Right portal vein embolization before right hepatectomy for unilobar colorectal liver metastases reduces the intrahepatic recurrence rate. Ann Surg 2006;244(1):71-9.
180. Pachler J, Wille-Jorgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. Cochrane Database Syst Rev 2005(2):CD004323.
181. Pahlman L, Bohe M, Cedermark B, et al. The Swedish rectal cancer registry. Br J Surg 2007;94(10):1285-92.
182. Palmer G, Martling A, Blomqvist L, Cedermark B, Holm T. Outcome after the introduction of a multimodality treatment program for locally advanced rectal cancer. Eur J Surg Oncol 2005;31(7):727-34.
183. Palmer G, Martling A, Cedermark B, Holm T. Preoperative tumour staging with multidisciplinary team assessment improves the outcome in locally advanced primary rectal cancer. Colorectal Dis 2011;13(12):1361-9.
184. Parazzini F, Braga C, La Vecchia C, Negri E, Acerboni S, Franceschi S. Hysterectomy, oophorectomy in premenopause, and risk of breast cancer. Obstet Gynecol 1997;90(3):453-6.
185. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. Obstet Gynecol 2009;113(5):1027-37.
186. Passot G, Glehen O, Pellet O, et al. Pseudomyxoma peritonei: role of 18F-FDG PET in preoperative evaluation of pathological grade and potential for complete cytoreduction. Eur J Surg Oncol 2010;36(3):315-23.
187. Persky H, Dreisbach L, Miller WR, et al. The relation of plasma androgen levels to sexual behaviors and attitudes of women. Psychosom Med 1982;44(4):305-19.
188. Pettersson D, Cedermark B, Holm T, et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg 2010;97(4):580-7.
189. Pettersson D, Holm T, Iversen H, Blomqvist L, Glimelius B, Martling A. Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. Br J Surg 2012.
190. Pfannenberg C, Konigsrainer I, Aschoff P, et al. (18)F-FDG-PET/CT to select patients with peritoneal carcinomatosis for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2009;16(5):1295-303.
191. Pieterse QD, Ter Kuile MM, Deruiter MC, Trimbos JB, Kenter GG, Maas CP. Vaginal blood flow after radical hysterectomy with and without nerve sparing. A preliminary report. Int J Gynecol Cancer 2008;18(3):576-83.

192. Platell CF, Thompson PJ, Makin GB. Sexual health in women following pelvic surgery for rectal cancer. Br J Surg 2004;91(4):465-8.
193. Pollack J, Holm T, Cedermark B, et al. Late adverse effects of short-course preoperative radiotherapy in rectal cancer. Br J Surg 2006;93(12):1519-25.
194. Portilla AG, Shigeki K, Dario B, Marcello D. The intraoperative staging systems in the management of peritoneal surface malignancy. J Surg Oncol 2008;98(4):228-31.
195. Potter JD, Slattery ML, Bostick RM, Gapstur SM. Colon cancer: a review of the epidemiology. Epidemiol Rev 1993;15(2):499-545.
196. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986;2(8514):996-9.
197. Ramsey SD, Andersen MR, Etzioni R, et al. Quality of life in survivors of colorectal carcinoma. Cancer 2000;88(6):1294-303.
198. Rayson D, Bouttell E, Whiston F, Stitt L. Outcome after ovarian/adnexal metastectomy in metastatic colorectal carcinoma. J Surg Oncol 2000;75(3):186-92.
199. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002;346(21):1616-22.
200. Rees PM, Fowler CJ, Maas CP. Sexual function in men and women with neurological disorders. Lancet 2007;369(9560):512-25.
201. Riley A, Riley E. Controlled studies on women presenting with sexual drive disorder: I. Endocrine status. J Sex Marital Ther 2000;26(3):269-83.
202. Ripley RT, Davis JL, Kemp CD, Steinberg SM, Toomey MA, Avital I. Prospective randomized trial evaluating mandatory second look surgery with HIPEC and CRS vs. standard of care in patients at high risk of developing colorectal peritoneal metastases. Trials 2010;11:62.
203. Rodrigues AC, Teixeira R, Teixeira T, Conde S, Soares P, Torgal I. Impact of pelvic radiotherapy on female sexuality. Arch Gynecol Obstet 2011.
204. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26(2):191-208.
205. Rubin J, Clawson M, Planch A, Jones Q. Measurements of peritoneal surface area in man and rat. Am J Med Sci 1988;295(5):453-8.
206. Ruhstaller T, Roe H, Thurlimann B, Nicoll JJ. The multidisciplinary meeting: An indispensable aid to communication between different specialities. Eur J Cancer 2006;42(15):2459-62.
207. Rymer J, Morris EP. "Extracts from "Clinical evidence": Menopausal symptoms. Bmj 2000;321(7275):1516-9.
208. Sadeghi B, Arvieux C, Glehen O, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer 2000;88(2):358-63.
209. Sakakura C, Hagiwara A, Yamazaki J, et al. Management of postoperative follow-up and surgical treatment for Krukenberg tumor from colorectal cancers. Hepatogastroenterology 2004;51(59):1350-3.
210. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26(12):2013-9.
211. Sanoff HK, Sargent DJ, Campbell ME, et al. Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741. J Clin Oncol 2008;26(35):5721-7.
212. Santoro N, Torrens J, Crawford S, et al. Correlates of circulating androgens in mid-life women: the study of women's health across the nation. J Clin Endocrinol Metab 2005;90(8):4836-45.
213. Sarnaik AA, Sussman JJ, Ahmad SA, Lowy AM. Technology of intraperitoneal chemotherapy administration: a survey of techniques with a review of morbidity and mortality. Surg Oncol Clin N Am 2003;12(3):849-63.
214. Scott N, Jamali A, Verbeke C, Ambrose NS, Botterill ID, Jayne DG. Retroperitoneal margin involvement by adenocarcinoma of the caecum and ascending colon: what does it mean? Colorectal Dis 2008;10(3):289-93.

215. Segelman J, Singnomklao T, Hellborg H, Martling A. Differences in multidisciplinary team assessment and treatment between patients with stage IV colon and rectal cancer. Colorectal Dis 2009;11(7):768-74.
216. Shen P, Thai K, Stewart JH, et al. Peritoneal surface disease from colorectal cancer: comparison with the hepatic metastases surgical paradigm in optimally resected patients. Ann Surg Oncol 2008;15(12):3422-32.
217. Shifren JL, Davis SR, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. Menopause 2006;13(5):770-9.
218. Sideris L, Zenasni F, Vernerey D, et al. Quality of life of patients operated on for low rectal cancer: impact of the type of surgery and patients' characteristics. Dis Colon Rectum 2005;48(12):2180-91.
219. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer 2006;94(7):982-99.
220. Simpson ER. Aromatization of androgens in women: current concepts and findings. Fertil Steril 2002;77 Suppl 4:S6-10.
221. Sobin LH GM, Wittekind C eds. New York, NY: John Wiley & Sons, Inc., ed. TNM Classification of Malignant Tumors. 7th ed.; 2010.
222. Socialstyrelsen. The National Board of Health and Welfare. *Cancer incidence in Sweden 2009*. http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18204/2010-12-17.pdf. 2010.
223. Socialstyrelsen. *The National Board of Health and Welfare*. Causes of Death 2007. In; 2007.
224. Socialstyrelsen. *The National Board of Health and Welfare.* Nationella riktlinjer för bröst-, kolorektal och prostatacancer, beslutsstöd för prioriteringar: Stockholm http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/8947/2007-102-9_200710291.pdf. 2007.
225. Socialstyrelsen. *The National Board of Health and Welfare.* Nationella riktlinjer för kolorektalcancersjukvård - Medicinskt och hälsoekonomiskt faktadokument. http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/8944/2007-102-3_20071024.pdf 2007.
226. Socialstyrelsen. *The National Board of Health and Welfare*. The Cancer Register. Cancer Incidence in Sweden 2007. In; 2007.
227. Sodergard R, Backstrom T, Shanbhag V, Carstensen H. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. J Steroid Biochem 1982;16(6):801-10.
228. Somboonporn W, Davis S, Seif MW, Bell R. Testosterone for peri- and postmenopausal women. Cochrane Database Syst Rev 2005(4):CD004509.
229. Sommariva A, Pilati P, Rossi CR. Cyto-reductive Surgery combined with Hyperthermic Intra-Peritoneal Chemotherapy for Peritoneal Surface Malignancies: Current treatment and results. Cancer Treat Rev 2011.
230. Sprangers MA, te Velde A, Aaronson NK. The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module (QLQ-CR38). European Organization for Research and Treatment of Cancer Study Group on Quality of Life. Eur J Cancer 1999;35(2):238-47.
231. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res 1980;40(2):256-60.
232. Suda Y, Ohta H, Makita K, Takamatsu K, Horiguchi F, Nozawa S. Influence of bilateral oophorectomy upon lipid metabolism. Maturitas 1998;29(2):147-54.
233. Sugarbaker PH. Intraperitoneal chemotherapy and cytoreductive surgery for the prevention and treatment of peritoneal carcinomatosis and sarcomatosis. Semin Surg Oncol 1998;14(3):254-61.
234. Sugarbaker PH. Management of peritoneal-surface malignancy: the surgeon's role. Langenbecks Arch Surg 1999;384(6):576-87.
235. Sugarbaker PH. Peritonectomy procedures. Ann Surg 1995;221(1):29-42.
236. Sugarbaker PH. Revised guidelines for second-look surgery in patients with colon and rectal cancer. Clin Transl Oncol 2010;12(9):621-8.

237. Sugarbaker PH, Alderman R, Edwards G, et al. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. Ann Surg Oncol 2006;13(5):635-44.
238. Sugarbaker PH, Jablonski KA. Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. Ann Surg 1995;221(2):124-32.
239. Sugarbaker PH, Van der Speeten K, Stuart OA. Pharmacologic rationale for treatments of peritoneal surface malignancy from colorectal cancer. World J Gastrointest Oncol 2010;2(1):19-30.
240. Tan KL, Tan WS, Lim JF, Eu KW. Krukenberg tumors of colorectal origin: a dismal outcome--experience of a tertiary center. Int J Colorectal Dis 2009;25(2):233-8.
241. Taylor FG, Quirke P, Heald RJ, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. Ann Surg 2011;253(4):711-9.
242. Tekkis PP, Cornish JA, Remzi FH, et al. Measuring sexual and urinary outcomes in women after rectal cancer excision. Dis Colon Rectum 2009;52(1):46-54.
243. Tjandra JJ, Kilkenny JW, Buie WD, et al. Practice parameters for the management of rectal cancer (revised). Dis Colon Rectum 2005;48(3):411-23.
244. Traa MJ, De Vries J, Roukema JA, Den Oudsten BL. Sexual (dys)function and the quality of sexual life in patients with colorectal cancer: a systematic review. Ann Oncol 2011.
245. Traish A, Guay AT, Spark RF. Are the Endocrine Society's Clinical Practice Guidelines on Androgen Therapy in Women misguided? A commentary. J Sex Med 2007;4(5):1223-34; discussion 34-5.
246. Traish AM, Kim N, Min K, Munarriz R, Goldstein I. Role of androgens in female genital sexual arousal: receptor expression, structure, and function. Fertil Steril 2002;77 Suppl 4:S11-8.
247. Tuiten A, Van Honk J, Koppeschaar H, Bernaards C, Thijssen J, Verbaten R. Time course of effects of testosterone administration on sexual arousal in women. Arch Gen Psychiatry 2000;57(2):149-53; discussion 55-6.
248. Van Cutsem E, Dicato M, Arber N, et al. Molecular markers and biological targeted therapies in metastatic colorectal cancer: expert opinion and recommendations derived from the 11th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2009. Ann Oncol 2010;21 Suppl 6:vi1-10.
249. Van Cutsem E, Kohne CH, Lang I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011;29(15):2011-9.
250. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011;12(6):575-82.
251. van Leeuwen BL, Graf W, Pahlman L, Mahteme H. Swedish experience with peritonectomy and HIPEC. HIPEC in peritoneal carcinomatosis. Ann Surg Oncol 2008;15(3):745-53.
252. Van Loon K, Venook AP. Adjuvant treatment of colon cancer: what is next? Curr Opin Oncol 2011;23(4):403-9.
253. Varban O, Levine EA, Stewart JH, McCoy TP, Shen P. Outcomes associated with cytoreductive surgery and intraperitoneal hyperthermic chemotherapy in colorectal cancer patients with peritoneal surface disease and hepatic metastases. Cancer 2009;115(15):3427-36.
254. Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer 2008;123(2):444-9.
255. Vermeulen A. Plasma androgens in women. J Reprod Med 1998;43(8 Suppl):725-33.
256. Verwaal VJ. Long-term results of cytoreduction and HIPEC followed by systemic chemotherapy. Cancer J 2009;15(3):212-5.

257. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2008;15(9):2426-32.
258. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21(20):3737-43.
259. West NP, Finan PJ, Anderin C, Lindholm J, Holm T, Quirke P. Evidence of the oncologic superiority of cylindrical abdominoperineal excision for low rectal cancer. J Clin Oncol 2008;26(21):3517-22.
260. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. J Clin Oncol 2010;28(2):272-8.
261. Whistance RN, Conroy T, Chie W, et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. Eur J Cancer 2009;45(17):3017-26.
262. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther 2005;31(1):1-20.
263. Wierman ME, Basson R, Davis SR, et al. Androgen therapy in women: an Endocrine Society Clinical Practice guideline. J Clin Endocrinol Metab 2006;91(10):3697-710.
264. Willett C, Tepper JE, Cohen A, Orlow E, Welch C. Obstructive and perforative colonic carcinoma: patterns of failure. J Clin Oncol 1985;3(3):379-84.
265. Vironen JH, Kairaluoma M, Aalto AM, Kellokumpu IH. Impact of functional results on quality of life after rectal cancer surgery. Dis Colon Rectum 2006;49(5):568-78.
266. Vlug MS, Laan ET, van Lunsen RH, van Koperen PJ, Polle SW, Bemelman WA. Genital and subjective sexual response in women after restorative proctocolectomy with ileal pouch anal anastomosis--a prospective clinical trial. J Sex Med 2010;7(7):2509-20.
267. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. N Engl J Med 1988;319(9):525-32.
268. Wolmark N, Rockette H, Mamounas E, et al. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. J Clin Oncol 1999;17(11):3553-9.
269. Wood JJ, Metcalfe C, Paes A, et al. An evaluation of treatment decisions at a colorectal cancer multi-disciplinary team. Colorectal Dis 2008;10(8):769-72.
270. Yan TD, Morris DL, Shigeki K, Dario B, Marcello D. Preoperative investigations in the management of peritoneal surface malignancy with cytoreductive surgery and perioperative intraperitoneal chemotherapy: Expert consensus statement. J Surg Oncol 2008;98(4):224-7.
271. Yang CC, Cao YY, Guan QY, et al. Influence of PDE5 inhibitor on MRI measurement of clitoral volume response in women with FSAD: a feasibility study of a potential technique for evaluating drug response. Int J Impot Res 2008;20(1):105-10.
272. Yoon FH, Perera F, Fisher B, Stitt L. Alterations in hormone levels after adjuvant chemoradiation in male rectal cancer patients. Int J Radiat Oncol Biol Phys 2009;74(4):1186-90.
273. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol 2011;29(28):3768-74.
274. Young-Fadok TM, Wolff BG, Nivatvongs S, Metzger PP, Ilstrup DM. Prophylactic oophorectomy in colorectal carcinoma: preliminary results of a randomized, prospective trial. Dis Colon Rectum 1998;41(3):277-83.
275. Young RH. From krukenberg to today: the ever present problems posed by metastatic tumors in the ovary: part I. Historical perspective, general principles, mucinous tumors including the krukenberg tumor. Adv Anat Pathol 2006;13(5):205-27.

APPENDIX

Female Sexual Function Index (FSFI) ©

Subject Identifier _____ Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

   ☐ Very high
   ☐ High
   ☐ Moderate
   ☐ Low
   ☐ Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Very high
   ☐ High
   ☐ Moderate
   ☐ Low
   ☐ Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Very high confidence
   ☐ High confidence
   ☐ Moderate confidence
   ☐ Low confidence
   ☐ Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Extremely difficult or impossible
   - ☐ Very difficult
   - ☐ Difficult
   - ☐ Slightly difficult
   - ☐ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

    - ☐ No sexual activity
    - ☐ Extremely difficult or impossible
    - ☐ Very difficult
    - ☐ Difficult
    - ☐ Slightly difficult
    - ☐ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

Thank you for completing this questionnaire