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COLORECTAL CANCER

ASPECTS OF MULTIDISCIPLINARY TREATMENT, METASTATIC DISEASE AND SEXUAL FUNCTION

Josefin Segelman

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To Jerker, Eira, Aina and Justus
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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.
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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>CEA</td>
<td>Carcinoembryonic antigen</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CME</td>
<td>Complete mesocolic excision</td>
</tr>
<tr>
<td>CRM</td>
<td>Circumferential resection margin</td>
</tr>
<tr>
<td>CRS</td>
<td>Cytoreductive surgery</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>EORTC QLQ</td>
<td>European Organization for Research and Treatment of Cancer Quality of Life Questionnaire</td>
</tr>
<tr>
<td>FAI</td>
<td>Female androgen insufficiency</td>
</tr>
<tr>
<td>FSFI</td>
<td>Female Sexual Function Index</td>
</tr>
<tr>
<td>HIPEC</td>
<td>Hyperthermic intraperitoneal chemotherapy</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>MDT</td>
<td>Multidisciplinary team</td>
</tr>
<tr>
<td>MRF</td>
<td>Mesorectal fascia</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PC</td>
<td>Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>PCI</td>
<td>Peritoneal Carcinomatosis Index</td>
</tr>
<tr>
<td>PET</td>
<td>Positron-emission tomography</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>SHBG</td>
<td>Sex hormone-binding globulin</td>
</tr>
<tr>
<td>SOE</td>
<td>Salpingo-oophorectomy</td>
</tr>
<tr>
<td>SOEB</td>
<td>Bilateral salpingo-oophorectomy</td>
</tr>
<tr>
<td>T</td>
<td>Testosterone</td>
</tr>
<tr>
<td>TME</td>
<td>Total mesorectal excision</td>
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</tbody>
</table>
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. 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. Incidence rates have increased slightly over the past decades (Fig. 1). 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.

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
Predictors for developing colorectal cancer include hereditary factors, advanced age, male sex, previous polyps or colorectal cancer, inflammatory bowel disease, obesity, and diabetes mellitus. 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. 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. Kindred and twin studies estimated that approximately 30% of all colorectal cancers are an inherited form of the disease. 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. The most frequently reported site for distant metastases is in the liver.
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. 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. 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.

Similarly 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%.
Ovarian metastases are reported to be associated with PC and to be more common
in relatively young women. The pathogenesis may be trancoelomic or lympho-vascular.

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. 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. The corresponding figures for rectal cancer were
64.1% and 60.9%. The strongest prognostic factor is tumour stage. In patients with localized
colorectal cancer, 5-year relative survival reaches 90%, compared to 5–15% in patients
with metastatic disease. 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.
Five-year survival after potentially curative resection of liver metastases ranges between
30% and 58%.

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. 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,
a median survival reaching 24 months \textsuperscript{171} \textsuperscript{211} \textsuperscript{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 \textsuperscript{70} \textsuperscript{154} \textsuperscript{258}. The rationale is to use the combination of cytoreductive surgery to treat macroscopic disease with perioperative intraperitoneal chemotherapy to treat microscopic disease \textsuperscript{238} \textsuperscript{239}. This is the only strategy that has shown curative results for PC in a randomized controlled trial and international register studies \textsuperscript{70} \textsuperscript{87} \textsuperscript{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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{72} \textsuperscript{79}.

\textbf{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 \textsuperscript{49} \textsuperscript{80} \textsuperscript{127} \textsuperscript{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 \textsuperscript{80} \textsuperscript{162} \textsuperscript{198}.

\textbf{Clinical Staging}

\textit{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, rigid 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) \textsuperscript{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 \textsuperscript{241}. Diffusion-weighted MRI is a promising method for distinguishing between tumour and fibrosis after radiochemotherapy \textsuperscript{107}. Recent data report improved selection of complete responders to neoadjuvant radiochemotherapy us-
ing diffusion-weighted MRI compared to standard pelvic MRI. 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. However, the technique is not accurate in the detection of mesorectal metastatic lymph nodes.

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. 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. The combination of functional PET data and detailed anatomical information provided by CT in dual modality PET/CT further improves staging accuracy. Early results with regard to aiding the selection of patients for CRS and HIPEC are promising. 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. Typically CT and MRI show unilocular or multilocular cystic masses, associated with variable degrees of solid components. 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. 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. 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. 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. In an international study, MDT assessment influenced decisions about staging methods and neo-adjuvant treatment of rectal cancer patients. Furthermore, in a study on treatment decisions at a colorectal cancer MDT, the vast majority of the decisions were implemented. 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. In a review examining the relationship between multidisciplinary care and patient survival, a significant positive association was reported in 12 of 21 studies, including 3 on colorectal cancer. 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. 

![Figure 3a. Proportion of patients assessed postoperatively by an MDT after elective surgery for colon cancer, 2007–2010, by region.](image)

![Figure 3b. Proportion of rectal cancer patients assessed by an MDT before treatment in Sweden, 2007-2010.](image)
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 edition221

<table>
<thead>
<tr>
<th>TNM classification 7th edition</th>
<th>TX</th>
<th>Primary tumour cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumour (T)</td>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td></td>
<td>Tis</td>
<td>Carcinoma in situ: intraepithelial or invasion of lamina propria</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>Tumour invades submucosa</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>Tumour invades muscularis propria</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>Tumour invades through the muscularis propria into the subserosa or pericoloecal fat</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
<td>Minimal invasion: &lt; 1 mm beyond the borders of the muscularis propria</td>
</tr>
<tr>
<td></td>
<td>T3b</td>
<td>Slight invasion: 1–5 mm beyond the borders of the muscularis propria</td>
</tr>
<tr>
<td></td>
<td>T3c</td>
<td>Moderate invasion: &gt;5–15 mm beyond the borders of the muscularis propria</td>
</tr>
<tr>
<td></td>
<td>T3d</td>
<td>Extensive invasion: &gt; 15 mm beyond the borders of the muscularis propria</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>Tumour penetrates to the surface of visceral peritoneum</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Tumour directly invades or is adherent to other organs or structures</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Regional lymph nodes (N)</td>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>Metastasis in 1–3 regional lymph nodes</td>
</tr>
<tr>
<td></td>
<td>N1a</td>
<td>Metastasis in one regional lymph node</td>
</tr>
<tr>
<td></td>
<td>N1b</td>
<td>Metastasis in 2–3 regional lymph nodes</td>
</tr>
<tr>
<td></td>
<td>N1c</td>
<td>Tumour deposit(s), i.e. satellites, in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>Metastasis in 4 or more regional lymph nodes</td>
</tr>
<tr>
<td></td>
<td>N2a</td>
<td>Metastasis in 4–6 regional lymph nodes</td>
</tr>
<tr>
<td></td>
<td>N2b</td>
<td>Metastasis in 7 or more regional lymph nodes</td>
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<td>--------------------------------</td>
<td>----</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Distant metastasis (M)</td>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td></td>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td></td>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td></td>
<td>M1a</td>
<td>Metastasis confined to one organ or site (for example liver, lung, ovary, non-regional node)</td>
</tr>
<tr>
<td></td>
<td>M1b</td>
<td>Metastases in more than one organ/site or the peritoneum</td>
</tr>
<tr>
<td>AJCC/UICC staging system</td>
<td>TNM classification 7th edition</td>
<td>Dukes’ classification</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Stage 0</td>
<td>Tis, N0, M0</td>
<td>-</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1–T2, N0, M0</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumour limited to bowel wall</td>
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<tr>
<td>Stage II</td>
<td>T3–4, N0, M0</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td><em>Stage IIA</em>: T3, N0, M0</td>
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<td></td>
<td><em>Stage IIB</em>: T4A, N0, M0</td>
<td></td>
</tr>
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<td></td>
<td><em>Stage IIC</em>: T4B, N0, M0</td>
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</tr>
<tr>
<td>Stage III</td>
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<td></td>
<td><em>Stage IIIA</em>:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1–T2, N1, M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1, N2a, M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Stage IIIB</em>:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3–T4a, N1, M0</td>
<td></td>
</tr>
<tr>
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<td>T2–T3, N2a, M0</td>
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<td></td>
<td>T1–T2, N2b, M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Stage IIIC</em>:</td>
<td></td>
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<tr>
<td></td>
<td>T4a, N2a, M0</td>
<td></td>
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<tr>
<td></td>
<td>T3–T4a, N2b, M0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4b, N1–N2, M0</td>
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<tr>
<td>Stage IV</td>
<td>Any T, Any, N M1</td>
<td>D</td>
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<tr>
<td></td>
<td><em>Stage IVA</em>: Ant T, Any N, M1a</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Stage IVB</em>: Any T, Any N, M1b</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>R0</th>
<th>No residual tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>Microscopic residual tumour</td>
</tr>
<tr>
<td>R2</td>
<td>Macroscopic residual tumour</td>
</tr>
</tbody>
</table>

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. 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.

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. The introduction of the TME technique has led to improved cancer-specific survival. 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. 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 theoretically more oncologically sound operation, as well as more accurate tumour staging. 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.

Anastomotic leakage is a common complication with high morbidity and occurs in about 9% of Swedish patients after anterior resection for rectal cancer. 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.

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.
If the tumour invades adjacent organs, an extended surgical procedure is necessary\textsuperscript{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\textsuperscript{1 3 4 5 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\textsuperscript{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\textsuperscript{27}. The Swedish national guidelines are based on this classification\textsuperscript{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)\textsuperscript{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\textsuperscript{189}. 
Figure 4. Neoadjuvant treatment of rectal cancer according to clinical stage. Modified from Blomqvist/Glimelius 27

<table>
<thead>
<tr>
<th>Favourable “good” group</th>
<th>Intermediate “bad” group</th>
<th>Advanced “ugly” group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid/upper rectum T1-T3b</td>
<td>Mid/upper rectum T3c/d</td>
<td>T4 with overgrowth to prostate, seminal vesicles, base of urinary bladder, pelvic side walls or floor, sacrum</td>
</tr>
<tr>
<td>Low rectum T1-2</td>
<td>Low rectum T3</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>T4 with peritoneal or vaginal involvement only</td>
<td>Positive lateral lymph nodes</td>
</tr>
<tr>
<td>MRF clear</td>
<td>MRF clear</td>
<td>MRF involvement (MRF+)</td>
</tr>
</tbody>
</table>

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).

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 palliative 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. 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.

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%. Survival is increased nearly to the same extent. Adding oxaliplatin to 5-FU/folinic acid reduces the risk of recurrence by another 10-15%. 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.

Adjuvant chemotherapy is recommended for stage III and "high-risk" stage II colon cancer patients, as the risk of recurrence is high (30–50%). Risk factors include fewer 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. In patients with unresectable stage IV colon and rectal cancer, palliative chemotherapy prolongs survival.

**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. An increased use of improved neoadjuvant chemotherapy protocols allows tumour downsizing and consequent resection. Advances in interventional radiology, in particular portal vein embolization and radiofrequency thermal ablation, have contributed to the management of patients with colorectal liver metastases. 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. 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, cholecystectomy, resection of the liver capsule, small bowel resection, colonic and rectal resection, gastrectomy, lesser omentectomy, pancreatic resection, hysterectomy, oophorectomy, and urinary bladder resection.

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). The tumour found at the time of surgical exploration of the abdomen is quantified using the peritoneal cancer index (PCI) by Sugarbaker. 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).

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 hepatitis, in order to avoid laparotomy in patients where complete CRS is not feasible. 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. 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. Median survival after inadequate cytoreduction is similar to that of palliative treatment only.

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. 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. This results in a higher concentration in the peritoneal cavity compared with plasma after intraperitoneal administration.

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

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. 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. 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. The open abdomen “Coliseum“ technique is used to administer HIPEC and the duration of perfusion is 30 minutes (Fig. 7).

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

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 hemorrhage. 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. 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. The procedure lacks scientific support, and it is not recommended in national guidelines today. In the only randomized trial on prophylactic 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. 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. Furthermore, SOE is a risk factor for osteoporosis, cardiovascular disease, and death.

**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. 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. 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. 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. In these patients, prophylactic SOE is an important component of ovarian cancer risk reduction. Furthermore, SOE before menopause reduces the risk of breast cancer in women with BRCA1/2 mutation as well as in the general population.

**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. However, previous studies have identified several sexual dysfunctions experienced by colorectal cancer survivors. Among men, these
include erectile dysfunction and ejaculatory disorders. Among women, specific sexual dysfunctions include dyspareunia, impaired sexual desire, arousal, lubrication, and orgasms.

Moreover, relatively non-specific problems such as decreased 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. Sexuality and intimacy are considered central to a person’s well-being and are important aspects of the quality of life. Poor sexual functioning and reduced sexual satisfaction are risk factors for a worse quality of life in cancer survivors.

In rectal cancer patients, preoperative radiotherapy, advanced age and complications to surgery are risk factors for postoperative sexual dysfunction. The type of surgery, presence of a stoma and low rectal tumours may also be associated with sexual dysfunction. While male sexual dysfunction after rectal cancer treatment has been well described, considerably less data have been published about the impact on women. 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. In men with rectal cancer treated with radiotherapy, subnormal serum levels of testosterone indicate permanent testicular dysfunction. 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.

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. 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). 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. 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). 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)
2. Adrenal (adrenal insufficiency, adrenalectomy)
3. Hypothalamic-pituitary (hypopituitarism)
4. Drug-related (GnRH agonists/antagonists, corticosteroids, oral contraceptives, oral estrogen treatment)
5. Idiopathic

According to a consensus statement, no commercially available assays are sufficiently sensitive or reliable for the low androgen levels in women. 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. Androgens are also involved in the genital physiological response through regulation of the smooth muscle and local blood flow. Increased vaginal blood flow after visual erotic stimulation has been demonstrated after sublingual testosterone administration. 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. Damage to autonomic nerves disrupt this process. 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. 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. A small number of studies report a direct relationship between serum levels of endogenous testosterone and sexual desire and coital frequency. However, other studies exploring the relationship between endogenous androgens and
sexual function have shown conflicting results. 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 DHEAS.

There is still much controversy and insufficient knowledge about Female Androgen Insufficiency (FAI). 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. 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.

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. In addition, improved sexual function, feelings of well-being, and mood have been reported following estradiol therapy in women with menopausal symptoms.
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

<table>
<thead>
<tr>
<th>Paper</th>
<th>Inclusion period</th>
<th>Follow-up until</th>
<th>Origin of the cohort</th>
<th>Study cohort</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1995/96–2004</td>
<td>2006</td>
<td>All inhabitants in the Stockholm region</td>
<td>All patients with stage IV colorectal cancer</td>
<td>1449 patients</td>
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<td>II</td>
<td>1995/96–2007</td>
<td>2010</td>
<td>All inhabitants in the Stockholm region</td>
<td>All patients with colorectal cancer of all stages</td>
<td>11,124 patients</td>
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<td>III</td>
<td>1995/96–2006</td>
<td>2008</td>
<td>All inhabitants in the Stockholm region</td>
<td>All women with colorectal cancer of all stages, without previous or synchronous gynaecological cancer</td>
<td>4566 female patients</td>
</tr>
<tr>
<td>IV</td>
<td>June 2008 – June 2011</td>
<td>Only baseline data</td>
<td>All 237 women with rectal cancer treated at any of the participating institutions.</td>
<td>Eligible women scheduled to undergo abdominal surgery for stage I–III rectal cancer who consented to join the study</td>
<td>82 female patients</td>
</tr>
</tbody>
</table>
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.
Patients and Methods

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 $\chi^2$ 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 necessary 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.\textsuperscript{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.\textsuperscript{149} Improved survival has also been reported for stage II–IV colorectal cancer patients after the inception of MDT conferences.\textsuperscript{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.\textsuperscript{43, 183} A positive association between MDT assessment and survival has also been reported for other malignancies in several studies.\textsuperscript{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.

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

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
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 chemo-therapeutics 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
similar to that previously reported \cite{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

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Values in parentheses are 95% confidence intervals unless indicated otherwise; * values are numbers of nodes examined; ** Within 3 months of the primary operation.
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, asymptomatic 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.\(^4\text{9} 14\text{7} 19\text{8} 24\text{0}\). 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.\(^4\text{9} 80\text{127}\). After complete resection of the malignant disease, reported 5-year disease-free and overall survival were 40% and 61%, respectively.\(^80\text{127}\). 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.

![Overall survival after R0 resection of stage I–III colon cancer, grouped according to recurrence. P < 0.001 (log rank test)](image-url)
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. 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.

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. Low response
rates to questionnaires or avoidance of specific items regarding sexual function is another important limitation, particularly in female patients. Response rates of less than 50% are common. 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 11. Flow-chart for inclusion in the study

All women with rectal cancer treated at the four study centres
n = 237

Did not meet the inclusion criteria, n = 71
Stage IV (verified or suspicion of), n = 43
Radiotherapy started before admission to study centre, n=21
Emergency surgery, n = 1
Local excision of primary tumour, n = 6

Women with stage I-III rectal cancer, scheduled to undergo abdominal surgery, n = 166

Exclusions n = 9
Not able to give informed consent, n = 5
Non-Swedish-speaking, n = 2
Short life-time expectancy, n = 2

Eligible for inclusion
n = 157

Not included, n = 75
Declined to join the study, n = 32
Not invited to join the study, n = 42
Unknown, n = 1

Included
n = 82

Incomplete responders to FSFI
n = 25

Included
n = 82

Complete responders to FSFI
n = 57

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
J. Segelman

corns dyspareunia and cannot be answered by women not including vaginal intercourse in their sexual activities \textsuperscript{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.

\textit{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 cancer 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 väl-definierad 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 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 föreknat 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-

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

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

Appendix
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*