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# **PREOPERATIVE STAGING AND RADIOTHERAPY IN RECTAL CANCER SURGERY**

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## ABSTRACT

**Background:** Rectal cancer affects approximately 2 000 people in Sweden every year. The overall survival rate is approximately 50% after five years. During the last decades the survival has increased and the local recurrence rate has declined. This can be attributed to improved surgical techniques and introduction of preoperative radiotherapy. The improved surgical technique includes specimen oriented surgery and introduction of the total mesorectal excision-technique (TME). The long-term complications of radiotherapy in rectal cancer are largely unknown. Prior to deciding on administration of preoperative radiotherapy, a preoperative staging is needed, using endorectal ultrasound, MRI or CT.

The aims of the present thesis were to determine the accuracy of endorectal ultrasonography in preoperative staging of rectal tumors and to evaluate the long-term consequences of preoperative radiotherapy in rectal cancer with or without TME-surgery.

**Patients & Methods.** The results from preoperative endorectal ultrasound staging of 545 patients with rectal tumors were compared with postoperative pathoanatomical staging. From 1980 through 1993, 1 406 patients were randomly assigned to either preoperative (5x5 Gy) radiotherapy and surgery, or to surgery alone, within the Stockholm I & II trials. These patients were operated with standard surgical technique prior to the TME-era. 139 of these patients were alive and available for follow-up at mean 14 years after surgery. Patients were examined with questionnaires regarding hospital admissions, medication used, bowel and urinary function and quality of life. Patients were also examined clinically, including rigid proctoscopy and anorectal manometry in those without a colostomy. Anorectal function in 68 patients operated with TME after a mean follow-up of 8 years was evaluated with identical questionnaires and examinations. Comparisons on anorectal function at long-term follow-up were made between patients operated with or without TME and with or without preoperative radiotherapy.

**Results:** The accuracy of endorectal ultrasound for preoperative staging was 69% for depth of bowel wall penetration with 13% of tumors understaged and 18% of tumors overstaged. The overall accuracy for perirectal lymph-nodes was 64% with 11% of tumors understaged and 25% overstaged. The accuracy for distinguishing a non-invasive from an invasive rectal tumor was 87%.

Patients treated with preoperative radiotherapy had significantly more cardiovascular disease, anal incontinence and urinary incontinence than patients treated with surgery alone. Patients operated with TME and preoperative radiotherapy had significantly more anal incontinence, compared to patients treated with TME alone. In a multivariate analysis of possible risk factors for developing anal incontinence, only preoperative radiotherapy was an independent risk factor (RR 2.78, 95% CI: 1.23-6.29). Patients with anal incontinence had a lower quality of life score compared to continent patients. The global QoL score did not differ between irradiated and non-irradiated patients.

**Conclusions:** Endorectal ultrasonography is useful in preoperative staging of rectal tumors. It identifies transmural invasion and reliably distinguishes between non-invasive and invasive rectal tumors.

Preoperative short-course, high-dose radiotherapy in rectal cancer increases the incidence of bowel, anal and urinary dysfunction, and may increase the risk for cardiovascular morbidity. The potential benefits of preoperative radiotherapy therefore need to be balanced against the risk for increased morbidity when tailoring the treatment for the individual patient.



# LIST OF PUBLICATIONS

The present thesis is based on the following papers, which will be referred to by their roman numerals as indicated below.

- I. **Accuracy of Endorectal Ultrasonography in Preoperative Staging of Rectal Tumors**  
Julio Garcia-Aguilar, Johan Pollack, Suk-Hwan Lee, Enrique Hernandez de Anda, Anders Mellgren, W. Douglas Wong, Charles O. Finne, David A. Rothenberger, Robert D. Madoff.  
*Dis Colon Rectum* 2002; 45: 10-15
- II. **Late Adverse Effects of Short-course Preoperative Radiotherapy in Rectal Cancer**  
Johan Pollack, Torbjörn Holm, Björn Cedermark, Daniel Altman, Bo Holmström, Bengt Glimelius, Anders Mellgren.  
*British Journal of Surgery*, 2006 in press
- III. **Long-term Effect of Preoperative Radiation Therapy on Anorectal Function**  
Johan Pollack, Torbjörn Holm, Björn Cedermark, Bo Holmström, Anders Mellgren.  
*Dis Colon Rectum* 2006; 49: 345-352
- IV. **Long-term Effect of TME-surgery and Preoperative Radiotherapy on Anorectal Function**  
Johan Pollack, Torbjörn Holm, Björn Cedermark, Bo Holmström, Anders Mellgren.  
*Submitted*

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## LIST OF ABBREVIATIONS

AJCC	American Joint Committee on Cancer
APR	Abdomino-perineal resection
AR	Anterior resection
ASCRS	American Society of Colon & Rectal Surgeons
CI	Confidence interval
CRM	Circumferential resection margin
CT	Computed tomography
EORTC	European Organisation for Research and Treatment of Cancer
ERUS	Endorectal ultrasonography
FSF	First sensation of rectal filling (anorectal manometry)
FU	Follow up
Gy	Gray (radiation dose)
LAR	Low anterior resection
MRI	Magnetic resonance imaging
MRP	Maximal resting pressure (anorectal manometry)
MSP	Maximal squeeze pressure (anorectal manometry)
MTV	Maximal tolerable volume (anorectal manometry)
NS	Not statistically significant ( $p=$ or $>0.05$ )
pN	Node status on pathoanatomical examination
pRT	Preoperative radiotherapy
pRT(+)	Treated with preoperative radiotherapy
pRT(-)	Treated without preoperative radiotherapy
pT	Tumor stage on pathoanatomical examination
pTNM	Tumor, Node and Metastases staging on pathoanatomical examination
PET	Positron emission tomography
QoL	Quality of Life
RAIR	Rectoanal inhibitory reflex
RT	Radiotherapy
SRCT	Swedish Rectal Cancer Trial
TME(+)	Treated with total mesorectal excision
TME(-)	Treated with old surgical technique
TNM	Tumor, Nodes, Metastasis (tumor classification system)
UICC	Union Internationale Contre le Cancer
uN	Node status with ERUS
US	Ultrasound
uT	Tumor stage with ERUS

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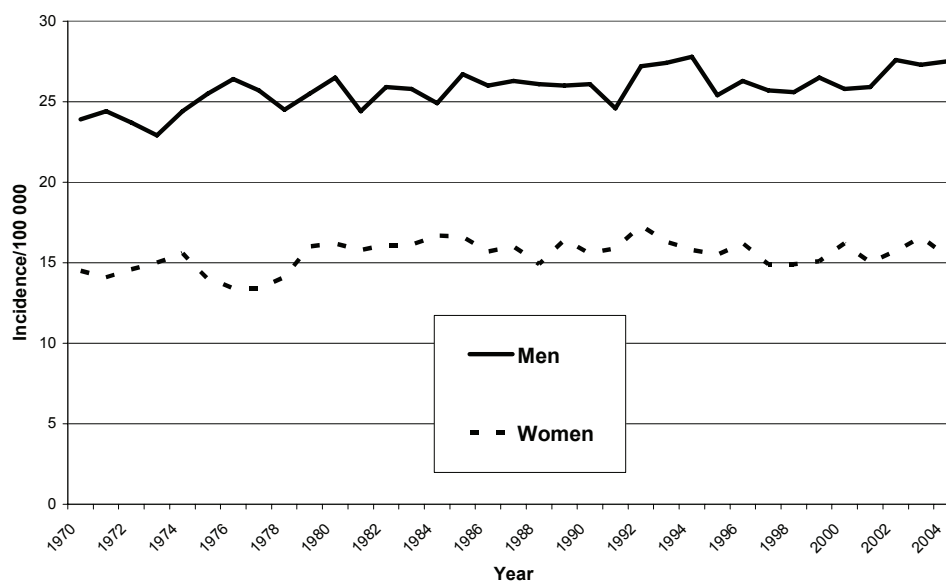


# 1 INTRODUCTION

## 1.1 EPIDEMIOLOGY AND ETIOLOGY

Colorectal cancer is the third most common cancer in the world. Globally about one million new cases are diagnosed each year and the annual incidence in Sweden is almost 5 000 new patients. About one third of colorectal cancers are located in the rectum (from the sacral promontory to the anal canal). The incidence has slowly increased during the last decades and rectal cancer is more common in men (Figure 1). The incidence in Sweden is 27.5 per 100 000 in men and 15.2 per 100 000 in women.

**Figure 1. Incidence of Rectal Cancer in Sweden 1970-2004**



The incidence of rectal cancer varies widely between different populations according to geographic region. In some African countries the annual incidence is less than 1 / 100 000. The difference seems not to be an effect solely from genetic factors since people migrating from low-incidence to high-incidence regions experience an increasing risk for developing rectal cancer (Greenfield *et al.*, 2001). Thus dietary factors have been proposed to play an important role in the development of the disease. In large population based studies, high fat intake and low fiber intake have been associated with an increased risk (Greenfield *et al.*, 2001). However conflicting results exist. In a recent meta-analysis including more than 700 000 patients with 6-20 years FU, no risk reduction from dietary fiber was found when other dietary factors were taken into account (Park *et al.*, 2005).

Based on studies on laboratory animals the carcinogenesis of adenocarcinoma in the colon and rectum has been described as an initiation-promotion process. The first step involves initiating factors that directly interacts with cellular DNA to induce mutations in the genome. A myriad of naturally occurring mutagens are introduced into the bowel through dietary intake. Some mutagens are also generated from interactions between the diet, microbial flora and enzymes. Mutagens typically

alkylate DNA at specific carbon residues and cause nucleotide misreading in the next cycle of DNA replication. The next promotion involves further growth and multiplication of the damaged mucosal cell. Promotion can be facilitated by dietary factors such as fat. Genetic predisposition also plays an important role in the pathogenesis. Several familial syndromes with an increased risk of developing colorectal carcinoma have been described (Grady *et al.*, 2005).

Cancers are proposed to evolve both de novo and from polyps in a stepwise fashion where an early adenoma eventually develops into an adenoma with high grade dysplasia. The adenoma can then develop high grade dysplasia and further to invasive cancer (Greenfield *et al.*, 2001).

Rectal cancer has two main routes for lymphatic spread. In the upper portion of the rectum, the route is upward along the superior rectal vessels to the inferior mesenteric vessels. The lower part of the rectum has an additional lateral lymphatic spread to lymph nodes along the internal iliac vessels. Spread downwards along the inferior rectal vessels to the groin can occur, but is rare, unless the anal canal is involved.

## **1.2 SYMPTOMS AND DIAGNOSIS**

The most common presenting symptoms in patients with rectal cancer are rectal bleeding, altered bowel habits, abdominal pain, bowel obstruction and tenesmus. Iron deficiency anemia can also be present (Greenfield *et al.*, 2001). Diagnosis is usually made by rectal examination including flexible or rigid sigmoidoscopy with multiple biopsies.

## **1.3 PREOPERATIVE STAGING**

Historically, rectal cancer was staged preoperatively with rigid sigmoidoscopy and digital rectal examination alone. The introduction of neoadjuvant treatments increase the demand on more detailed preoperative staging and several modalities are currently used for this assessment.

The first step in staging of a rectal tumor remains digital rectal examination if the tumor is reachable with the finger. The tumor can then be classified as mobile or fixed and according to location; anterior, posterior or lateral. The tumor consistency can also be judged as soft, nodular or hard. The relationship to adjacent organs can also be assessed.

To enhance the staging accuracy, additional staging methods such as ERUS, CT and MRI can be added to the digital rectal examination.

### **1.3.1 Pathoanatomical staging**

Historically, rectal cancer was staged with the Dukes' classification system proposed by Sir Cuthbert Dukes in 1932 (Dukes, 1932). This classification is based on the depth of penetration by the tumor into the bowel wall and presence of regional lymph node metastases or not. Dukes' stage A tumors are confined to the bowel wall and do not penetrate through the muscularis layer, stage B tumors penetrates through the rectal wall and stage C tumors have regional lymph node metastases. The definition of Dukes' D tumors has been added later and is used for tumors with

metastases to distant organs. The classification of colorectal cancer has been modified several times and the most widely used classifications are currently the AJCC/UICC classification and the TNM-system. The relationships between Dukes' AJCC/UICC and the TNM-system are shown in Table 1.

**Table 1.** Classification of rectal cancer

AJCC/UICC	Dukes'	TNM
I	A	T <sub>1-2</sub> N <sub>0</sub> M <sub>0</sub>
II	B	T <sub>3-4</sub> N <sub>0</sub> M <sub>0</sub>
III	C	T <sub>any</sub> N <sub>1-2</sub> M <sub>0</sub>
IV	D	T <sub>any</sub> N <sub>any</sub> M <sub>1</sub>

T<sub>1</sub>: Tumor infiltrates through the mucosa into the submucosa. T<sub>2</sub>: Tumor infiltrates into, but not through the muscularis propria. T<sub>3</sub>: Tumor infiltrates through the muscularis propria layer into the serosa or mesorectal fat. T<sub>4</sub>: Tumor infiltrates through the bowel wall into the peritoneal cavity or into adjacent organs. N<sub>0</sub>: No lymph node metastases. N<sub>1</sub>: 1-3 pericolic / perirectal nodes contain metastases. N<sub>2</sub>: >3 pericolic/perirectal nodes contain metastases. M<sub>0</sub>: No distant metastases. M<sub>1</sub>: Distant metastases present.

Moreover, preoperative assessment of the circumferential resection margin (CRM) is important for prognosis and for planning the treatment. The circumferential resection margin is the distance between the tumor edge and the border of the mesorectum. A narrow or involved CRM signifies an increased risk for local recurrence (Adam *et al.*, 1994).

### 1.3.2 Endorectal ultrasonography

During recent years endorectal ultrasonography (ERUS) has become a common diagnostic modality for local staging of rectal cancer. However, its accuracy, reliability, and validity are still controversial. Most studies include less than 100 patients and often represent only the initial institutional experience with the technique. Several studies on the accuracy of ERUS have been published. ERUS is highly accurate for T-staging, especially in benign lesions and early tumors, but less accurate for N-status. (Tables 2 and 3)

#### *Three dimensional endorectal ultrasonography*

For a three dimensional (3D) representation of the rectum and mesorectum a series of 2D images are put together. The series of 2D images are obtained by introducing the ultrasound probe through the anus and up above the tumor. The probe is surrounded by a rubber balloon which is then filled with degassed water for acoustic coupling between the transducer and the rectal wall. The probe is then retracted passing the tumor at a steady speed, acquiring a series of transverse pictures of the tumor, the rectal wall and the mesorectum. The series of pictures is then put together into a 3D representation. This technique is gaining increasing popularity and in a recent comparative study on 86 patients examined with 3D-ultrasound, 2D-ultrasound and CT, 3D-ERUS was superior in both T-staging and N-staging (Kim *et al.*, 2006). The accuracy for T-staging was 78% compared to 69% for 2D-ERUS in that series and N-

staging was accurate in 65% compared to 56%. Compared to previous studies on ERUS, the accuracy of 3D-ERUS was comparable to conventional 2D-ERUS.

**Table 2.** Accuracy of 2D-ERUS in the assessment of rectal wall invasion

Author	Patients	Accuracy	Overstaged	Understaged
Hildebrandt <i>et al.</i> , 1986	76	88%	12%	1%
Beynon <i>et al.</i> , 1987	49	90%	6%	4%
Holdsworth <i>et al.</i> , 1988	36	86%	3%	11%
Katsura <i>et al.</i> , 1992	120	92%	4%	3%
Herzog <i>et al.</i> , 1993	118	89%	10%	1%
Nielsen <i>et al.</i> , 1996	100	85%	5%	10%
Nishimori <i>et al.</i> , 1998	70	76%	7%	17%
Massari <i>et al.</i> , 1998	75	91%	4%	5%
Adams <i>et al.</i> , 1999	70	74%	7%	19%
Blomqvist <i>et al.</i> , 2000	49	59%	10%	31%

**Table 3.** Accuracy of 2D-ERUS in the diagnosis of lymph node metastasis

Author	Patients	Accuracy
Holdsworth <i>et al.</i> , 1988	36	61%
Beynon <i>et al.</i> , 1989	95	83%
Herzog <i>et al.</i> , 1993	111	80%
Akasu <i>et al.</i> , 1997	164	77%
Massari <i>et al.</i> , 1998	75	76%
Adams <i>et al.</i> , 1999	70	83%
Blomqvist <i>et al.</i> , 2000	47	60%

### 1.3.3 Magnetic Resonance Imaging

MRI has the potential for high-resolution images. Especially if an external pelvic phased-array coil or an endorectal coil is used, the resolution in the pelvis is greatly enhanced. The different layers of the rectal wall can be separated making an accurate T-staging possible. In previous studies (Beets-Tan *et al.*, 2004) the accuracy for T-staging was as high as for ERUS and varied between 71% and 92%. MRI with an endorectal coil has the same limitation of range of field as ERUS, the resolution rapidly drops outside the mesorectum, as the distance from the coil increases. The positioning of the coil in the rectum can also be difficult in patients with high and stricturing tumors. With pelvic phased-array coils, the resolution outside the rectal wall has improved substantially and the examination is less inconvenient for the patient. The endorectal coil has lately been superseded by the pelvic phased coil and is now less used for rectal cancer staging. Errors in T-staging mainly occur with differentiation between T2 and T3 tumors due to difficulties in distinguishing between reactive changes in the mesorectum and tumor growth into the mesorectum. N-stage accuracy with MRI is comparable to ERUS. With high-resolution MRI, lymph nodes as small as

2-3 mm can be detected, but the differentiation between normal, reactive and metastatic lymph nodes remains a radiological challenge.

MRI supplemented with pelvic phased coils can visualize the CRM between the tumor edge and the border of the mesorectum preoperatively (Brown *et al.*, 2005). This information is very useful for planning surgery and neoadjuvant treatment.

#### **1.3.4 Computed tomography**

Even though ERUS is the most widely used modality for preoperative staging of rectal cancer, CT has the advantage to be able to image the whole pelvic area including organs adjacent to the rectum. Distant metastases in the abdomen can also be detected at the same examination. The accuracy for CT in determining T-stage is less than for ERUS. The accuracy for CT has been reported to vary between 52-74%, and in a recent review the accuracy in more than 4 000 patients was 73% (Beets-Tan and Beets, 2004). The resolution on standard CT-scan is lower than with ERUS and the different layers of the rectal wall can not be readily separated with standard CT-scanning. This might be a reason for the lower accuracies for T-staging with CT.

In different reports the accuracy for N-staging with CT varies widely between 22-73% (Beynon *et al.*, 1989). The detection of lymph node metastases with radiological methods depends on changes in shape and size of lymph nodes. It is not possible to differentiate between a lymph node enlarged of reactive inflammation and a lymph node with metastasis on a CT-scan-picture alone. Newer modalities with PET-scanning might increase the ability to differentiate between metastatic and reactive lymph node enlargement (Gearhart, 2006).

#### ***Positron Emission Tomography – Computed Tomography***

Currently PET-CT scanning has no established role in preoperative staging of rectal cancer. The possibility to combine morphological and functional imaging might improve the accuracy for detecting lymph nodes involved with metastases. PET-CT scanning is currently under evaluation for imaging of local recurrences.

#### ***Summary preoperative staging***

ERUS is an accurate method for local staging of benign rectal tumors and early rectal cancer. For evaluation of the mesorectal fascia and the Circumferential Resection Margin (CRM) MRI with pelvic phased-array coils is currently the most reliable tool. For invasion into to neighboring organs spiral CT and MRI have comparable accuracy. For detection of local lymph nodes, ERUS and MRI are comparable. PET-CT might be an option for N-staging. CT has the advantage of being able to detect distant metastases in remote organs with a single scan, but the resolution is not enough for T-staging.

## 1.4 TREATMENT

In Sweden the 5-year survival in rectal cancer has gradually improved during the last decades. In fact, the 5-year survival in rectal cancer is now even better than for colon cancer (Anonymous VI, 2005). The cancer-specific 5-year survival is at present 70% compared to 50% some decades ago. (Glimelius, 2002) Until the early 1990s, surgery was the standard treatment. Currently after the large RT trials, which were conducted during the 1980s and 1990s, adjuvant RT and/or chemotherapy treatment is often used in conjunction with surgery (Kapiteijn *et al.*, 2001). Advances in surgical technique and the use of adjuvant treatment probably account for this improvement in survival. However, the mainstay treatment of rectal cancer is surgical en-bloc resection of the tumor with its lymphatic and vascular supply. RT can be an adjunct in eliminating microscopic foci of disease.

### 1.4.1 Surgery

During most of the 20<sup>th</sup> century a combined abdominal and perineal surgical approach to rectal tumors was utilized and the patient had to have a permanent end-colostomy. AR with colorectal anastomosis, and thus avoiding the need for a stoma, was later introduced. For early rectal cancer (T1-T2 N0 M0) local excision can be considered.

#### *Abdominoperineal resection*

In an APR operation, the rectum and its vascular and lymphatic supply is dissected and mobilized from an abdominal incision down to the pelvic floor. The dissection is then continued from the perineum and the total excision of the rectum and anal canal is completed. A permanent end colostomy is constructed in the left iliac fossa. Before introduction of the TME-technique (see below), the rectum was usually mobilized with blunt dissection.

#### *Anterior resection*

For cancers in the upper two thirds of the rectum AR with colorectal anastomosis has been used. Dissection was then performed from the abdomen, the rectum was divided and a colorectal anastomosis was constructed. The anastomosis was originally hand sewn, thus allowing only high rectal cancers to be treated with AR. With the introduction of a circular stapling device, even low rectal cancers could be treated with AR. Resection with the anastomosis constructed onto the distal part of the rectum or to the anal canal is labeled low AR. With APR and (L)AR as described above the local recurrence rates varied between centers, but were generally high and up to 50% (Rich *et al.*, 1983).

#### *TME-surgery*

Therefore, a surgical technique known as total mesorectal excision (TME) was developed to reduce the local recurrence (Heald *et al.*, 1986). High ligations of the inferior mesenteric vessels, near the aorta are done to encompass the lymph nodes

along the vessels. The left colonic flexure is usually mobilized to enable a tension-less colorectal anastomosis. The key point in the dissection is the development of the avascular plane between the rectum with the mesorectum and surrounding tissues including autonomic nerves. Sharp dissection using diathermy or scissors under direct vision is used throughout and conventional blunt manual extraction is avoided. When the whole rectum and mesorectum have been encompassed in this way the rectum and mesorectum can be divided usually 2-3 cm above the pelvic floor using a right-angled stapler. A colorectal anastomosis can then be constructed with a circular stapler introduced through the anus.

With this surgical technique local recurrence rates have been reported to be well below 10% in population based series (Martling *et al.*, 2000).

#### ***Local excision and other local treatment***

Local excision of early rectal cancer is an option if the tumor is small and accessible from below with an operating proctoscope or with transanal endoscopic microsurgery (TEM). In patients with poor surgical risk, unsuitable for abdominal surgery other options are local destruction with electrocautery and endocavitary irradiation

### **1.4.2 Radiotherapy**

RT for rectal cancer can be given prior to (neoadjuvant) or after (adjuvant) the surgical resection to decrease local recurrence and possibly also increase survival. Different treatment regimens have been utilized. Preoperative RT has been shown to be superior to postoperative RT in terms of local control (Frykholm-Jansson, 1993, Sauer *et al.*, 2004). Different fractionations have also been tested. In Sweden preoperative 5x5 Gy fractionation with surgery the following week has become the standard RT regimen based on the results from the SRCT and the Stockholm I and II trials (Cedermark *et al.*, 1995, Anonymous, 1997, Martling *et al.*, 2001). About half of all patients treated in Sweden for rectal cancer are currently treated with pRT (Anonymous VI, 2005). Short-course pRT with immediate surgery is convenient for the patient and can be used for patients with potentially resectable rectal cancer. For locally advanced rectal cancer, with overgrowth to adjacent organs, preoperative chemoradiation with longer treatment periods may be beneficial and induce down-sizing and down-staging prior to surgery (Moesta *et al.*, 2006). The aim of pRT is to eliminate microscopic foci of disease in the pelvis.

Even though the pRT has been shown to improve local control and possibly also survival, the optimal fractionation has not been established. Longer treatment period with smaller daily doses than in the Swedish trials have also been studied (usually 2 Gy fractions 10-20 times) (Glimelius, 2003). No comparative studies exist between these fractionations. The two ways of fractionation have different advantages and disadvantages with regard to anti tumor effect and tissue toxicity. High dose fractionation may cause more long-term complications compared to fractionations with lower daily doses. The other important determinator for toxicity is the irradiated volume. Initially large volumes were irradiated but the irradiated volume has gradually been reduced. Postoperative RT has the advantage of selective use according to the



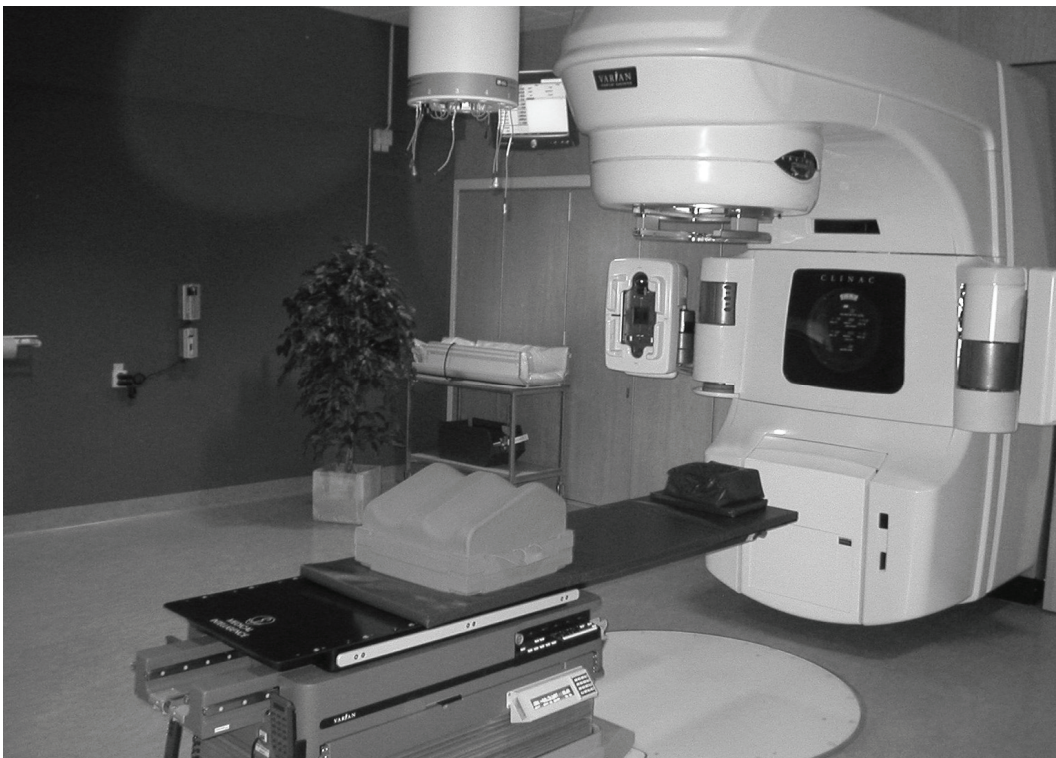
pathoanatomical examination of the surgical specimen and thus a more reliable staging can be used as basis for decisions on RT administration. One disadvantage is the possibility for more small bowel toxicity due to small bowel falling into the pelvis after removal of the rectum. A reliable preoperative staging, as with ERUS or MRI, is therefore desirable.

### *Radiation technique*

Radiotherapy is currently administered with linear accelerators using 8-16 MegaVolt photons with a four-field technique. A computerized dose-planning system is used to define the target volume based on the preoperative staging of the tumor. The sphincters are shielded in high rectal tumors. The radiation field was originally shielded with lead shields. At present the linear accelerators have collimators that can be used to customize the irradiated volume to the individual patient. (Figure 2)

In the Stockholm I trial, a two field technique was used extending from the L2 vertebra down to and below the anal verge. In the Stockholm II trial the radiation regimen was changed to a four-field technique and the upper border was lowered to the L4 vertebra. In the SRCT (Anonymous V, 1997) and the Uppsala trial (Frykholm-Jansson G, 1996) a 5x5 Gy radiation regimen using a four-field technique was also used.

**Figure 2.** Linear accelerator for radiotherapy treatment.





### *Complications to radiotherapy*

Early reactions to RT become evident during the treatment or within the first three months after treatment and include skin reactions, gastrointestinal, genitourinary and neurological complications. A scoring system has been developed by the Radiation Therapy Oncology Group that can be used for grading of complications (Trotti, 2003). In this system there is a six grade scoring ranging from 0-5. Where 0 represents no complaints and 5 represents toxicity leading to death. With the 5x5 Gy pRT currently in use, the acute effects are usually mild and self-limiting. A few patients develop more severe reactions with proctitis, or pain in the gluteal region or legs secondary to neurological damage (Frykholm-Jansson G, 1996).

In FU of the Stockholm I and II trials, Holm (1996) reported increased number of hip and pelvic fractures after RT in the Stockholm I trial. Irradiated patients in the Stockholm II trial had increased number of venous thromboembolism and enterocutaneous fistulas. Irradiated patients in the Stockholm I and II trials also had more episodes of small bowel obstruction compared to non-irradiated patients. At short-term FU of patients in the Stockholm I study an increased mortality in cardiovascular events was noted in especially in elderly patients (Holm *et al.*, 1996).

Pelvic irradiation may also increase the risk for secondary malignancies. In long-term FU of the SRCT, Birgisson, *et al.* (2005) reported an increased number of tumors in patients treated with pRT. However the difference was not significant for tumors within the pelvis. In a population based study on men treated for prostate cancer, an increased number of rectal cancers were reported in patients treated with RT (Baxter, *et al.*, 2005).

FU of patients in the SRCT and the Dutch TME-trial have shown impaired anorectal function in irradiated patients and, in the Dutch TME trial, irradiated patients also had impaired sexual function (Dahlberg *et al.*, 1998, Marijnen *et al.*, 2005). Reports on complications after 5x5 Gy pRT at long-term FU (more than 10 years) is sparse.

### **1.4.3 Chemotherapy**

Chemotherapy can be used as neoadjuvant treatment in locally advanced rectal cancer (T3-T4 or N1-2) alone or together with pRT. Preoperative chemoradiation is standard of care in several countries for locally advanced rectal cancer (Glynne-Jones *et al.*, 2006). Chemotherapy can also be used alone or in combination with RT in the postoperative setting. The aims of chemotherapy treatment are:

1. To enable secondary curative resection or decrease the local recurrence rate through preoperative treatment –neoadjuvant therapy.
2. To prevent local recurrence and metastatic disease after complete surgical resection –adjuvant treatment.
3. To prolong survival, control symptoms and improve QoL in metastatic disease –palliative treatment.

Leucovorin and fluorouracil have been the standard drugs for palliation of metastatic colorectal cancer. Lately new drugs, like oxaliplatin and irinotecan, have been established as both first and second line therapy. Targeted treatments

with monoclonal antibodies and tyrosine kinase inhibitors are currently under evaluation in metastatic colorectal cancer.

#### **1.4.4 Specimen Oriented Management**

The management of rectal cancer patients has in the last decade improved and the concept of specimen orientated surgery is gaining increasing popularity. In the Stockholm County a collaborative group called the Stockholm Colorectal Cancer Study Group was assembled in 1980. Since then the group consisting of specialists in colon and rectal surgery, radiology, pathology and oncology has conducted several trials and also implemented a quality control system with a registry including all colorectal cancer patients in greater Stockholm. The registry includes data on tumor stage, type of surgery and adjuvant treatment and also FU after surgery according to a FU protocol. The Stockholm I and II trials were initiated and conducted by members of the group. Currently the Stockholm III study is running, comparing short- and long-course pRT with immediate or delayed surgery.

The rectal cancer patient is currently treated by a team of specialists in colon and rectal surgery, radiology, pathology, oncology and specialist nurses. After the rectal cancer diagnosis is made, the patient is further investigated for staging of the tumor including detection of possible metastases. Special attention is put to the invasiveness of the tumor at the border of the mesorectum and the possibility to achieve a negative circumferential margin is a key issue for decision on adjuvant treatment (Burton *et al.*, 2006). An individual treatment plan, including type of surgical procedure and possible neoadjuvant therapy, is made for each patient. After surgery the specimen is divided in gross sections and examined in collaboration between pathologist and surgeon (Quirke, 2003). When the patient has recovered after surgery a decision on possible postoperative chemotherapy is made in a multi professional conference based on patient and tumor characteristics (Moesta and Kockerling, 2006).

### **1.5 PROGNOSIS**

#### *Survival*

Tumor stage is an important factor influencing the prognosis of rectal cancer. Patients with Stage I rectal cancer have 95% five-year survival rate while patients with stage IV rectal cancer have a 5-year survival rate below 20%. During the last decades the relative five-year survival rate in Sweden has increased from 50% to 70% (Anonymous VI, 2005). The increase in survival has mainly been attributed to improved surgery, implementation of pRT and management with specimen oriented surgery.

Approximately 10 to 15% of all newly diagnosed patients with rectal cancer have a tumor that has grown into adjacent, non-readily resectable organs. These patients are generally considered as primarily non-resectable. Approximately 15–20% of the patients have already developed distant metastases (stage IV, Dukes' D) at the time of diagnosis (Anonymous VI, 2005). After completion of apparently curative surgery, the two main reasons for fatal outcome are occult distant metastases not found at surgery and local recurrence.

### *Local recurrence*

With old surgical technique, the local recurrence rates were reported between 20-50% (Cedermark *et al.*, 1985). With TME-technique the local recurrence rates can be decreased substantially. Series with local recurrence rates below 5% with TME-surgery alone have been reported (Heald *et al.*, 1998). In the Dutch TME-trial, the local recurrence rate was 11% in the surgery alone group and 4% in the surgery plus RT group at four-years FU (Marijnen *et al.*, 2003). In Sweden the local recurrence rate is now 8% in population based registries (6% in patients operated on with curative surgery and pRT and 10% in patients treated with curative surgery alone (Anonymous VI, 2005. There are also reports pointing to the importance of the individual surgeon for the outcome (Martling *et al.*, 2002).

A local recurrence or a primary non-resectable rectal cancer is accompanied by severe suffering for the patient with pain, bleeding, soiling, ulceration and fistulation with impaired QoL (Peeters *et al.*, 2003).

### *Metastases*

The most important reason for failure and death in rectal cancer patients is the development of distant metastases. The most common sites are the liver and lungs. Only few patients are amenable for cure since most have disseminated disease with several metastases. Metastases to the liver and lungs may however be accessible for surgical excision or other local treatment. Chemotherapy is currently under evaluation and but has so far only been proven to have limited and palliative effect.



## **2 AIMS**

The aims of the present thesis were to:

1. Review a single institution experience with ERUS and to determine its accuracy in discriminating between early and advanced rectal tumors. (Paper I)
2. Assess if ERUS is useful for selection of patients for local treatment and pRT. (Paper I)
3. Assess long-term morbidity and QoL in patients undergoing rectal cancer surgery with or without preoperative short course RT. (Paper II)
4. Assess late effects on anorectal function after anterior resection for rectal cancer with or without pRT. (Paper III)
5. Compare anorectal function at long-term FU in patients treated with LAR with TME-surgery or AR with traditional surgery with or without pRT. (Paper IV)



## 3 PATIENTS

### 3.1 THE STOCKHOLM I & II TRIALS

The Stockholm I & II trials were two large randomized prospective trials conducted between 1980-1993 evaluating pRT in rectal cancer (Cedermark *et al.*, 1995, Anonymous IV, Martling *et al.*, 2001). Together these trials included 1,406 patients with a biopsy-proven adenocarcinoma of the rectum judged resectable for cure with an abdominal procedure. Patients with distant metastases, locally advanced cancer, previous RT to the pelvis or patients scheduled for local excision were excluded from the studies (Holm *et al.*, 1995). Patients were randomized to rectal resection with or without pRT and hospitals in the Stockholm County and on the island of Gotland participated in the studies.

The Stockholm I trial included 849 patients with clinically resectable rectal tumors diagnosed from 1980 through February 1986. In patients randomized to pRT a total dose of 25 (5x5) Gray (Gy) was administered using a two-field technique. The beam limits extended from the L2 vertebra down to below the anal verge, and the target included the rectum, the perirectal tissues, the anal sphincters and the regional lymph nodes (inguinal, paravertebral and the obturator foramina).

In the Stockholm I trial the local recurrence rate was reduced by 50% (25% vs. 12%) in irradiated patients, but this group also had an increased 30-day mortality rate which was most pronounced in elderly patients (Cedermark *et al.*, 1995).

The Stockholm II trial included 557 patients 1986 – 1993. In this study the protocol was slightly changed. A four-field box-technique was used and a smaller volume was irradiated (beam limits were from the L4 vertebra and down to and including the anal canal). In addition, the upper age limit was 80 years. With these changes, irradiation still had a significant effect on local control. The 30-day postoperative mortality was higher in the irradiated group (2% vs. 1%) however this difference was not statistically significant (Martling *et al.*, 2001).

### 3.2 THE TME-TRIAL

In an attempt to decrease the local recurrence rates an educational initiative to introduce the TME technique in Stockholm was launched in 1994. Three workshops lasting 3-4 days each were held at the Karolinska Hospital in Stockholm. The majority of surgeons treating rectal cancer patients in Stockholm at that time participated in all three workshops. Ample time was allocated for discussions around pre-recorded videos describing the technique and also around live-surgery demonstrations via high-quality video link. Each participant also assisted Professor R. J. Heald or Professor B. J. Moran, from the North Hampshire Colorectal Research unit, Basingstoke, UK. Two histopathology sessions were also included.

During 1995-96 447 patients were treated for rectal cancer in the Stockholm area by TME-trained surgeons. Data on these patients were prospectively registered into a database and have been described earlier (Martling *et al.*, 2000).

### **3.3 PAPER I**

Consultant colorectal surgeons at the University of Minnesota have used ERUS for preoperative staging since the 1980s. The charts of 1184 patients with rectal adenocarcinoma or villous tumors treated at the University of Minnesota were reviewed. All patients were staged by ERUS and operated by the staff members of the Division of Colon and Rectal Surgery at the University of Minnesota over a 10-year period. A total of 639 patients were excluded from the analysis for different reasons including preoperative radiation therapy and treatment by snare polypectomy. Of the 545 patients included in the study, 238 underwent radical surgery (APR or LAR) and 307 underwent local excision of their rectal tumors. There were 273 males and 272 females and mean age was 67 (range 25-98) years.

### **3.4 PAPER II**

In June 2002, 252 patients out of the 1406 patients treated within the Stockholm I and II trials were still alive. A letter was sent to these 252 patients asking them to fill out questionnaires regarding their medical history and QoL. Responding patients were asked to come for a clinical FU visit. Patients not responding received two repeat questionnaires and remaining non-responders were contacted by telephone.

Sixty-eight patients declined participation, 26 patients were not able to participate because of impaired mental or physical condition and eleven because of geographical reasons (not living in the Stockholm region). Eight patients died before the questionnaires were returned.

Thus, 139 patients were alive, available for FU and agreed to participate in the study. The mean FU time was 15 (range 9-21) years. Mean age at FU was 74 (range 48-89) years. Forty-five patients were originally included in the Stockholm I study and 94 patients in the Stockholm II study. Sixty-five patients (29 women) had been treated with pRT and surgery and 74 patients (35 women) had been treated with surgery alone. An AR had been performed in 64 patients and an APR in 75 patients.

### **3.5 PAPER III**

In June 2002, 119 patients out of 528 patients originally treated with LAR in the Stockholm I and II trials were still alive. These patients were contacted as in Paper II and asked to complete a questionnaire regarding their medical history, bowel habits and QoL. The patients were also asked to come for a clinical FU visit.

Sixty-four patients were alive, without a stoma, and agreed to participate in the study. Fifty-five patients did not participate in the study of the following reasons: Five patients had undergone reoperations with permanent colostomy, two because of a new cancer, one because of anastomotic dehiscence, and two because of small bowel obstruction. Thirteen patients were not able to participate because of impaired mental or physical condition, six because of geographic reasons (not living in the Stockholm region) and 25 declined participation. Six patients died before the questionnaires and examinations were completed.

Of the 64 participating patients, 21 had received pRT and 43 had been treated with surgery alone. Four of the 64 participating patients fulfilled the questionnaires, but declined physical examination because of their physical condition. Mean FU-time was 14 (range, 9-23) years. Mean age at FU was 75 (range 51-93) years. Patient characteristics were evenly distributed between the radiated and the non-irradiated



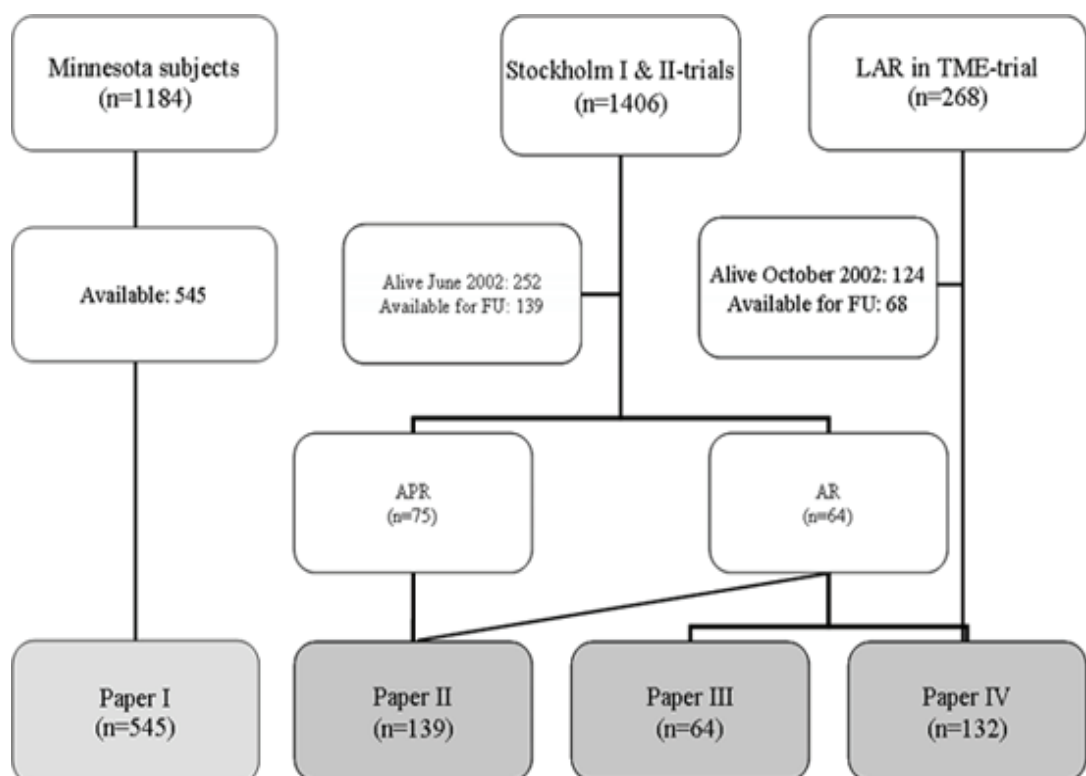
groups, but a larger proportion of patients in the non-irradiated group had had Stage III cancer. Sixty-one patients had end-to-end anastomoses and three patients (one patient treated with RT and two treated with surgery alone) had side-to-end anastomoses.

### 3.6 PAPER IV

In all 268 patients were treated with LAR during 1995-1996 within the TME-trial. One-hundred and fifty of them were treated with pRT and 118 patients with surgery alone. The decision to administer RT was made by the surgeon and the patient, thus no randomization of RT was used. Of these patients, 147 patients were alive in October 2002. These were contacted and asked for participation in a FU-study in the same way as described for paper III above.

Paper IV focuses on the 124 patients treated with LAR that were alive and without a stoma at the time of FU. Of these 124 patients five patients had moved outside the Stockholm area, twelve patients could not participate because of mental or physical inability. Twelve patients died before the questionnaires and examinations were completed and 27 patients declined participation. Thus 68 patients were included into the study. Twenty-four of the 68 participating patients returned the questionnaires, but declined physical examination due to their physical limitations. Mean FU-time was 8 (range, 6-10) years. Mean age at FU was 73 (range 36-90) years. Forty-five of the patients had been treated with pRT and 23 with surgery alone. These 68 patients were compared with the 64 patients operated on with old surgical technique included in Paper III.

**Figure 3.** Recruitment base of patients in papers I-IV.





## **4 METHODS**

### **4.1 QUESTIONNAIRES (PAPER II-IV)**

#### **4.1.1 Anorectal function**

A questionnaire regarding general health, medications used and surgery done since the diagnoses of rectal cancer was answered by all patients in Paper II - IV. A shortened version of a bowel function questionnaire developed by the Swedish Society of Colorectal Surgeons was also included with questions regarding bowel function and anal incontinence (Hallbook *et al.*, 2000). Fecal incontinence was defined as involuntary leakage of liquid or solid feces. Fecal incontinence was graded into three different levels: once a week or less, more than once a week but not daily, and daily. Appendix A includes a copy of the questionnaire translated into English.

#### **4.1.2 Quality of Life**

Quality of life with respect to fecal incontinence was evaluated with the American Society of Colon & Rectal Surgeons (ASCRS) QoL questionnaire (FiQL) (Rockwood *et al.*, 2000). The four different scales represent different aspects of life. Scores from a set of questions are summed up and a mean score is calculated for each scale and patient. Patients operated with AR or LAR in Paper II-IV answered this questionnaire. The questionnaire can be found in Dis Colon & Rectum 2000;43(1);9-16.

QoL was also analyzed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ C30 (Aaronson *et al.*, 1993). This instrument consists of six functional scales with one global health scale, and physical, role, social, emotional and cognitive function scales. It also has nine symptom scales and single item symptom scores. All responses were linearly transformed to give a score from 0 to 100. For multi item (functional) scales, a higher score indicates a higher level of functioning. For symptom scales (single items and multi items), a higher score indicates more symptoms. The QLQ C-30 was answered by all patients in Paper II-III.

### **4.2 CLINICAL EXAMINATION (PAPER II-IV)**

All patients underwent a clinical examination with abdominal palpation, including examination for hernias or intra-abdominal masses. Patients operated on with AR/LAR were also examined with digital rectal palpation and rigid proctoscopy. Rectal examination with digital palpation and rigid proctoscopy was carried out in the left lateral position. Patients were asked to clean the rectum with a small enema one hour prior to the examination. Rigid proctoscopy was performed to exclude abnormalities, as proctitis or local recurrence, and to measure the distance between the anal verge and the anastomosis. The diameters of the anastomoses were classified as possible to pass with the rigid proctoscope or not. The diameter of the proctoscope used was 17 mm.

### 4.3 ENDORECTAL ULTRASONOGRAPHY (PAPER I)

Patients examined with ERUS (Paper I) were examined with a triad of diagnostic modalities: digital examination, proctoscopy, and ERUS. The patients were prepared for the examination with a Fleets® enema one hour before the ERUS (C.B. Fleet Company™, Inc., Lynchburg, USA). The patients were examined in a left lateral position. The tumor, if reachable, was palpated with the finger to assess mobility and then inspected through the rigid proctoscope. A 7-MHz or a 10-MHz endosonographic probe (Type 3535, B & K™, Naerum, Denmark) was introduced through the proctoscope. The probe, covered with a rubber balloon, was carefully passed from the anal verge to the upper rectum. The balloon was then filled with variable amounts of water to achieve optimal contact with the rectal wall, and the probe was slowly retracted passing the tumor. The results of the clinical and endosonographic examination were documented in a formalized form and then fed into a database. At ERUS, the uT-stage was classified according to a five-layer model of the rectal wall and the uT classification proposed by Hildebrandt *et al.*, (1986) was used. (Table 4)

**Table 4.** Staging of rectal tumors with endorectal ultrasound

Stage	Description
<b>uT0</b>	Confined to mucosa
<b>uT1</b>	To, but not trough, submucosa
<b>uT2</b>	Into, but not trough muscularis, propria
<b>uT3</b>	Through bowel wall into perirectal fat
<b>uT4</b>	Involving adjacent structures
<b>uN0</b>	No definable lymph nodes by ultrasound
<b>uN1</b>	Ultrasonographically apparent lymph nodes

Pathologic lymph nodes were defined as circular or slightly oval shaped structures, often with an irregular border, and with an echogenicity similar to the tumor, as proposed by Beynon *et al.* (1989).

The surgeon decided the treatment strategy based on tumor and patient characteristics. The surgical specimens were sent for pathoanatomical examination and staging according to the pTNM classification. The pararectal lymph nodes were classified as free from metastatic disease (pN0) or as with metastatic spread (pN1), thus no discrimination between N1 and N2 was done in the comparison. The ultrasound images were compared with the postoperative pathoanatomical stage. The tumor status (T-stage) was compared in all included patients (n=545) and the node status (N-stage) was compared in patients undergoing radical surgery (n=238). The tumor was classified as overstaged if the pathoanatomical examination showed a lower T- or N-staging compared to the ERUS staging. If the ERUS staging had a higher T- or N-staging than the pathoanatomical staging on the surgical specimen, the tumor was classified as understaged.

#### 4.4 ENDOANAL ULTRASOUND (PAPER III)

Endoanal ultrasound was performed using a 10 MHz endosonographic probe (Type 3535, B & K™, Naerum, Denmark). A hard, sonolucent plastic cap with a diameter of 17 mm covered the transducer and was filled with degassed water for acoustic coupling. The cup was covered with a rubber condom and was carefully introduced through the anus and passed up to the rectum and then retracted to the anal verge.

The result of the endosonographic examination was documented with pictures printed from the upper, mid and distal anal canal. The upper anal canal was defined as the level of the puborectalis muscle, the middle anal canal as the level with circular internal and external anal sphincters and the distal anal canal was defined as the level where only the external anal sphincter was present.

The endosonographic criterion for diagnosis of anal sphincter injury, i.e. a discontinuity in the muscle ring, was the detection of a distinct change in ultrasonic appearance from the remaining anal sphincter ring. Sphincter injuries were documented by measuring the angle of the sector from the center of the probe. Scarring of the sphincters was defined as one or more hypo- or hyperechogenic areas in the internal and/or external sphincter.

**Figure 4.** The author is preparing an ultrasound examination.



#### 4.5 ANORECTAL MANOMETRY (PAPER III-IV)

Anorectal manometry was performed using a water perfused manometry system and the Synectics Polygram® version 2.2 software (Medtronic Diagnostics™, Minneapolis, USA). Patients were asked to empty the rectum with a Micro-Lax® (Pfizer, Sollentuna, Sweden) enema one hour prior to examination. Examination was



performed with the patient in the left lateral position. A stationary pull-through technique with an eight-channel water-perfused catheter was used. Anal resting and squeeze pressures were recorded at each cm starting at six cm from the anal verge. The mean pressures of all eight channels were calculated at each level and thereafter the maximal resting pressure (MRP) and the maximal squeeze pressure (MSP) were calculated from the mean pressures at each centimeter in the distal three centimeters of the anal canal. The first sensation of rectal filling and the maximal tolerable volume (MTV) of the rectum or the neorectum were registered by insufflating air in a rectal balloon with the lowest part six cm from the anal verge. Mean pressures and mean volumes were calculated for each group studied e.g. pRT(+) and pRT(-).

**Figure 5.** The author is ready to start an anorectal manometry examination.



## 4.6 STATISTICAL ANALYSES

All statistical analyses were made with the JMP<sup>®</sup> 5.1 statistical software (SAS Institute Inc. <sup>TM</sup> Cary, NC, USA). Fischer's exact test or a chi-square test was used accordingly to compare prevalence of symptoms. Independent samples t-test was used in ANOVA-analyses for continuous variables i.e. manometric measurements and QoL scores. In Paper IV a multivariate logistic regression model was used for analyzing the potential impact of TME-surgery, pRT and anastomotic dehiscence on anorectal function. A *p*-value of less than 0.05 was considered statistically significant.

## 4.7 ETHICAL APPROVAL

The University of Minnesota Institutional Review Board (IRB) approved the study in Paper I and the studies in Paper II-IV were approved by the Karolinska Institutet local Ethics Committee.

## 5 RESULTS

### 5.1 PREOPERATIVE STAGING WITH ENDORECTAL ULTRASONOGRAPHY

Overall accuracy of ERUS in assessing the depth of tumor penetration in the rectal wall (T stage) was 69 %, with 18 % of the tumors overstaged and 13 % understaged (Table 5).

**Table 5.** Accuracy of ERUS in T- and N-staging.

Stage	Accuracy	Overstaged	Understaged
uT	69%	18%	13%
uN	64%	25%	11%

The accuracy of ERUS in T-staging was highest for benign lesions 87% and varied between 50% and 70% for cancer lesions. (Table 6).

**Table 6.** Rectal wall invasion: ERUS (uT) vs. pathoanatomical examination.

Stage	Accuracy	Overstaged	Understaged
uT0	87 %	-	13%
uT1	47 %	32 %	21%
uT2	68 %	16 %	16%
uT3	70 %	28 %	2%
uT4	50%	50 %	-
Total	69%	18%	13%

For transmural invasion the positive predictive value was 72 %, and the negative predictive value was 93 %. The accuracy of ERUS in distinguishing between a non-invasive and an invasive tumor was 87 %, while the accuracy in distinguishing between a tumor localized in the rectal wall versus a tumor penetrating into the perirectal fat was 88 % (Table 7).

**Table 7.** Accuracy of ERUS in the diagnosis of submucosal and transmural invasion of rectal tumors.

	<b>Submucosal Invasion</b>	<b>Transmural Invasion</b>
<b>Accuracy</b>	87%	88%
<b>Sensitivity</b>	77%	78%
<b>Specificity</b>	95%	91%
<b>Positive predictive value</b>	87%	72%
<b>Negative predictive value</b>	90%	93%

The accuracy of ERUS in the diagnosis of lymph node metastasis in the 238 patients who underwent radical surgery without preoperative radiation therapy was 64 % (Table 8). The sensitivity for nodal involvement was 33 %, but the specificity was 82 %. The positive predictive value was 52 % and the negative predictive value was 68 %.

**Table 8.** Lymph node metastasis: ERUS (uN) vs. pathoanatomical examination.

<b>Stage</b>	<b>Accuracy</b>	<b>Overstaged</b>	<b>Understaged</b>
<b>un0</b>	68%	-	32%
<b>uN1</b>	52%	48%	-
<b>Total</b>	64%	25%	11%



## 5.2 LONG-TERM MORBIDITY AFTER PREOPERATIVE RADIOTHERAPY

Overall, irradiated patients had some type of adverse event more often than non-irradiated patients (69 % vs. 43 %;  $p=0.002$ ) (Table 9). When analyzing Stockholm I and II separately, the difference between irradiated and non-irradiated patients was statistically significant in the Stockholm II study, but not in the Stockholm I trial. Few patients had been treated with the two-field RT technique utilized during the Stockholm I trial.

**Table 9.** Adverse events in patients treated with and without preoperative RT.

Adverse event	pRT(+) (n=65)	pRT(-) (n=74)	<i>p</i> -value
Any adverse event in Stockholm I & II	45 (69%)	32 (43%)	<0.01
Any adverse event in Stockholm I (pRT(+) n=24, pRT(-) n=21)	13 (54%)	9 (43%)	0.55
Any adverse event in Stockholm II	32 (78%)	23 (43%)	<0.01
Cardiovascular disease	23 (35%)	14 (19%)	0.03
Urinary incontinence	29 (45%)	20 (27%)	0.02
Incomplete bladder emptying	17 (26%)	13 (18%)	0.19
Venous thrombo-embolism	4 (6%)	5 (7%)	0.82
Small bowel obstruction	19 (29%)	13 (18%)	0.07
Hip and pelvic fractures	3 (5%)	1 (1%)	0.23

In the irradiated group, significantly more patients reported a history of cardiovascular disease than in the non-irradiated group (35 % vs. 19 %,  $p=0.032$ ). Eight patients reported intermittent claudication, two of them had been treated with surgery alone. Signs of local atherosclerosis in the pelvic arteries were evident in six patients treated with pRT and in two patients in the surgery alone group. Three of the six patients with intermittent claudication after pRT, had no other signs of cardiovascular disease. The number of patients with vascular disease occurring within the irradiated volume did not significantly differ between irradiated and non-irradiated patients ( $p=0.146$ ). These data were verified with hospital charts in a sample of seventeen patients.

There was no statistical difference in the number of episodes of venous thrombo-embolism between irradiated and non-irradiated patients. More patients had been treated for small bowel obstruction in the irradiated group, but this difference was not statistically significant ( $p=0.074$ ). Urinary incontinence was more common in irradiated patients (45 % vs. 27 %,  $p=0.023$ ), but there were no significant differences in the frequency of bladder emptying difficulties or in the frequency of sexual inactivity. There was no statistically significant difference in prevalence of urinary incontinence between patients operated on with AR or APR (46 vs. 54 %,  $p=0.591$ ). More patients reported bone fractures during the FU-time in the irradiated group, but the difference was not statistically significant ( $p=0.118$ ).

Assessment of QoL with the EORTC QLQ C-30 questionnaire is shown in Figures 6-7, Table 10-11. Figure 6 show QoL-scores in patients without a colostomy. In patients without a colostomy, irradiated patients reported significantly higher

scores on diarrhea symptoms than did non-irradiated patients ( $p=0.002$ ). None of the other scales differed significantly between irradiated and non-irradiated patients without a colostomy. Figure 7 shows QoL-scores in patients with a colostomy. No significant differences were found between irradiated and non-irradiated patients with colostomy. QoL scores were also compared between irradiated and non-irradiated patients. Irradiated patients scored significantly lower on social functioning (79 vs. 87,  $p=0.045$ ) and scored higher on pain (29 vs. 21,  $p=0.049$ ) compared with non-irradiated patients. Pain in the pelvic area was not significantly more common among irradiated patients.

There were only minor differences in QoL-scores between the study population and a sample from the Swedish population (Table 10) (Michelson *et al.*, 2000). However, only mean values were available from the general population, thus no statistical comparisons could be calculated.

When comparing AR-patients with APR-patients, AR patients scored significantly higher on the physical function score (84 vs. 75,  $p=0.015$ ). None of the other scales in the QLQ C30-questionnaire differed between AR and APR patients.

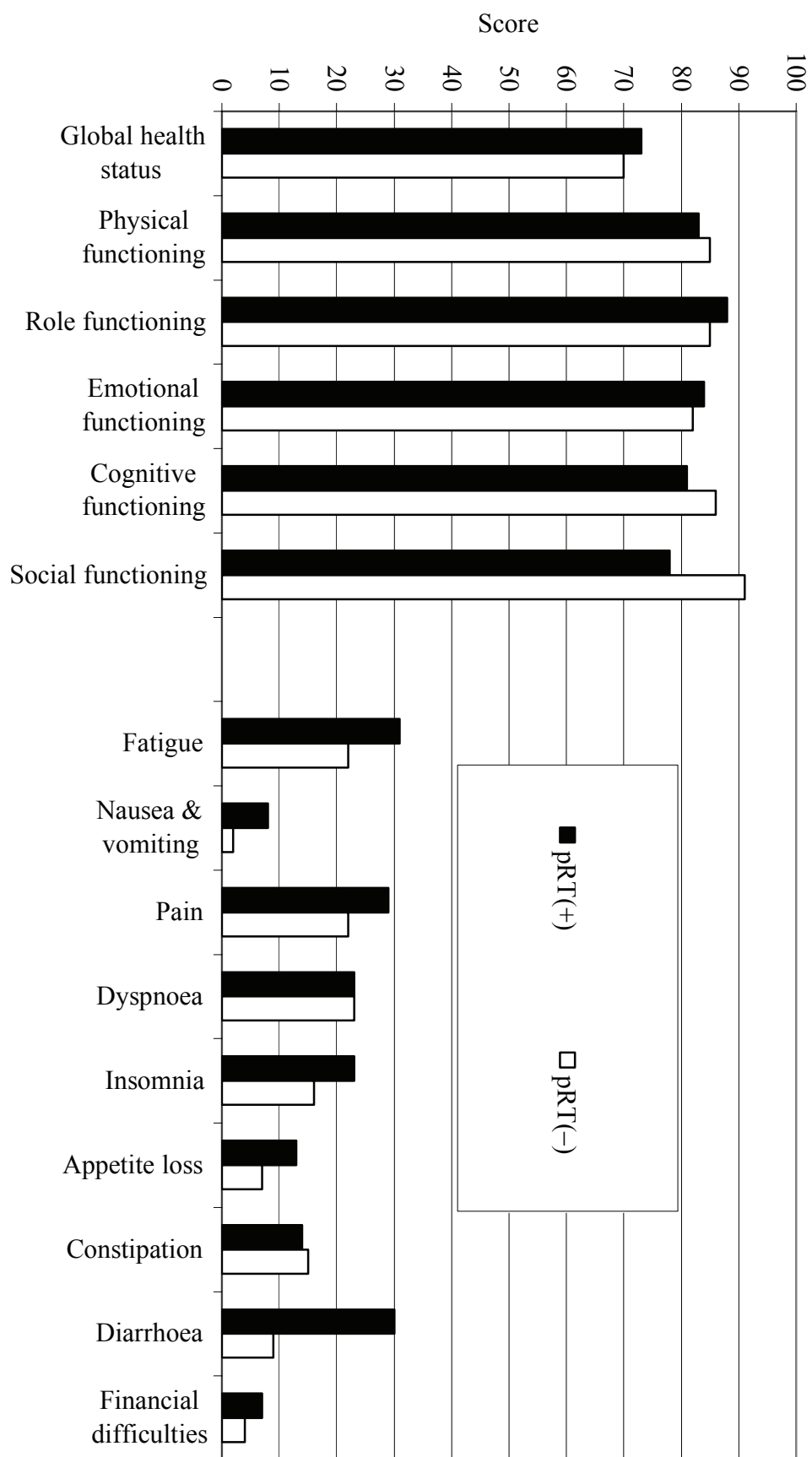
**Table 10.** QoL scores in the study population and in the general Swedish population.

Scale	pRT(+)	pRT(-)	General population*
Global health status	71	69	73
Physical functioning	75	80	78
Role functioning	77	81	82
Emotional functioning	82	84	84
Cognitive functioning	81	83	85
Social functioning	79	87	90
Fatigue	31	26	25
Nausea & vomiting	7.5	2.9	3.1
Pain	29	20	23
Dyspnoea	27	21	23
Insomnia	24	19	19
Appetite loss	11	6	5.0
Constipation	9.3	11.5	7.7
Diarrhoea	21	15	4.6
Financial difficulties	9.8	4.2	6.8

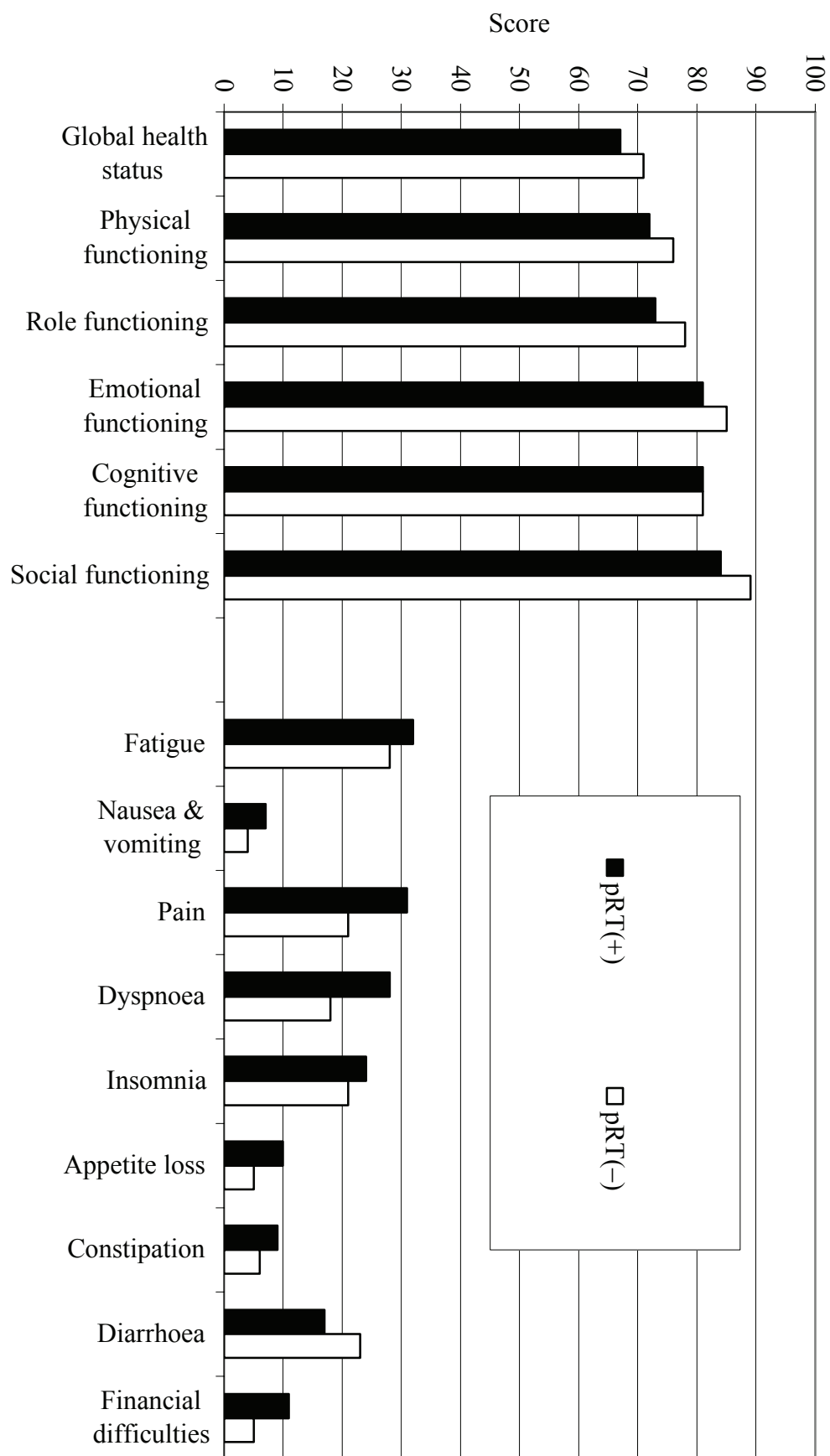
When comparing QoL scoring between male and female patients, female patients scored significantly lower on four of the six functional scales. Female patients had a significantly higher score on 4/9 symptom scales. Table 11.

**Table 11:** QoL scores in the study population, comparison of male and female patients.

<b>Scale</b>	<b>Female</b>	<b>Male</b>	<b><i>p</i>-value</b>
Global health status	65	73	0.04
Physical functioning	72	83	<0.01
Role functioning	73	84	0.05
Emotional functioning	74	89	<0.01
Cognitive functioning	82	82	0.88
Social functioning	82	85	0.56
Fatigue	34	23	0.02
Nausea & vomiting	8.6	3.5	0.07
Pain	33	17	<0.01
Dyspnoea	26	19	0.18
Insomnia	28	15	0.02
Appetite loss	11	7.0	0.27
Constipation	18	6.6	<0.01
Diarrhea	21	16	0.39
Financial difficulties	10	3.9	0.10



**Figure 6.** QoL in non-colostomy patients



**Figure 7. QoL in patients with colostomy**

### 5.3 ANORECTAL FUNCTION AFTER ANTERIOR RESECTION

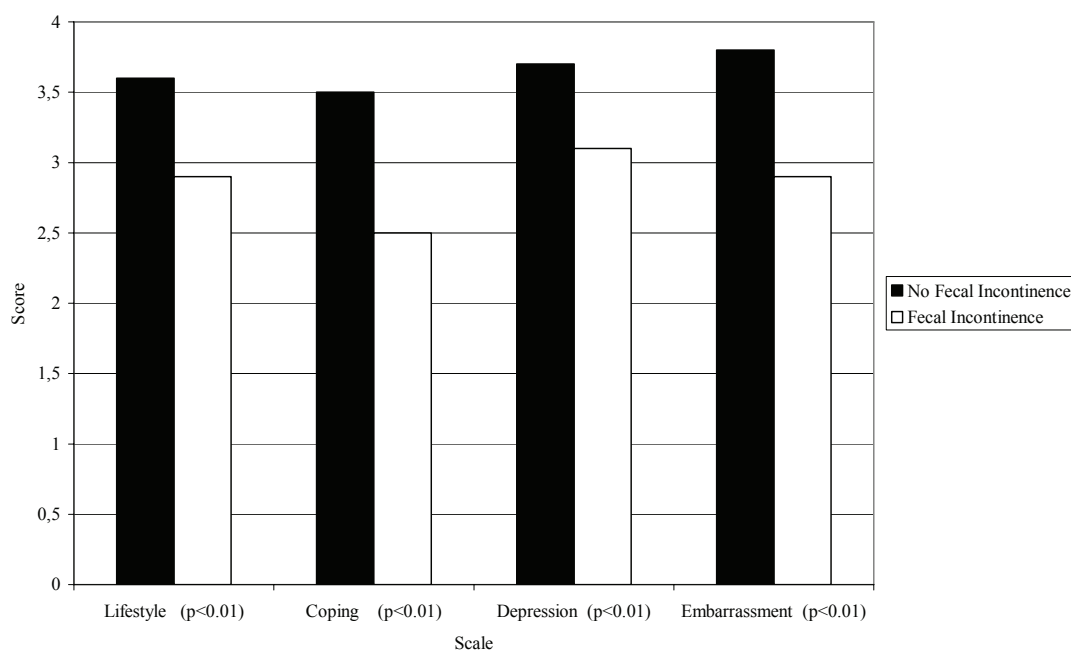
At FU of patients treated with AR with or without RT within the Stockholm I & II trials, fecal incontinence, gas incontinence and soiling were significantly more prevalent in the irradiated group than in the surgery alone group (Table 12). Patients in the irradiated group also had significantly more frequent bowel movements than patients in the surgery alone group (Table 12). Patients in both groups frequently reported that they had a gradual improvement of anal incontinence during the first years after surgery.

Patients with anal incontinence had been treated previous to the FU in the present study by their regular surgeon with conservative regimens. No patient had been treated with surgery for their anal incontinence.

Few patients had been treated with two-field RT and there were no significant differences in continence impairment between the two slightly different radiation regimens in the Stockholm I (n=4) and II (n=17) trials.

The fecal incontinence QoL score showed no significant differences between irradiated and non-irradiated patients in any of the scales. The fecal incontinence QoL score was however significantly lower in incontinent patients than in continent patients in all four scales (Fig. 8).

**Figure 8** Quality of life scores on fecal incontinence in continent vs. incontinent patients.



**Table 12.** Anorectal function after anterior resection.

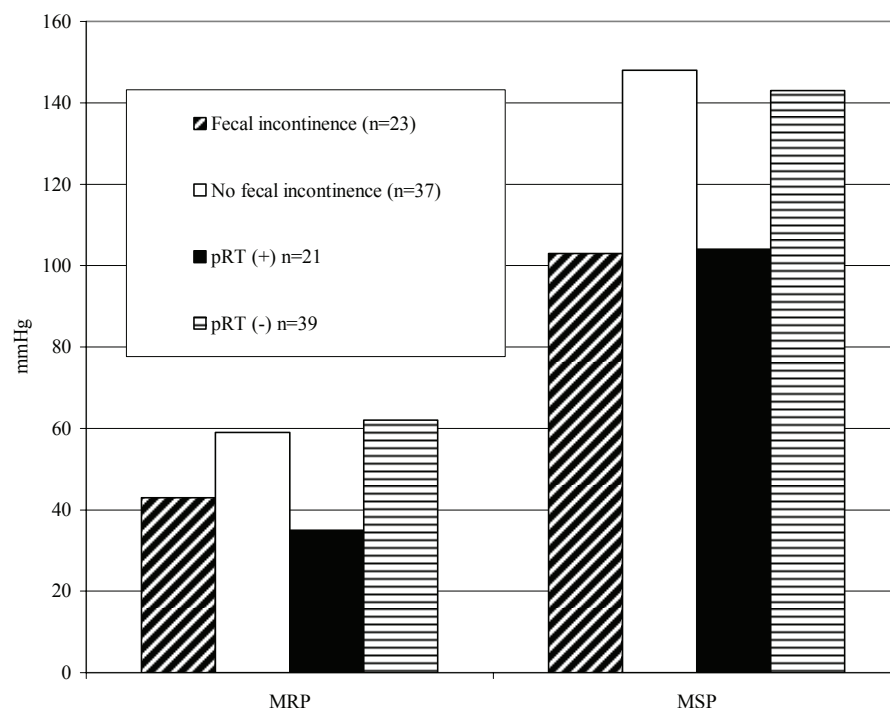
	pRT(+) n=21	pRT(-) n=43	<i>p</i> -value
Fecal incontinence	12 (57%)	11 (26%)	0.01
Gas incontinence	15 (71%)	17 (46%)	0.03
Soiling	8 (38%)	6 (16%)	0.04
Stool frequency per week (range)	20 (2-50)	10 (1-49)	0.02

One patient in the irradiated group and two patients in the non-irradiated group had small incisional hernias at physical examination. No patient had palpable intra abdominal masses or pathologically enlarged lymph nodes in either group.

Mean anastomotic height from the anal verge was ten (range, 5-12) cm in the irradiated group and nine (range 3–14) cm in the non-irradiated group (N.S.). The anastomosis was not possible to identify at proctoscopy in four irradiated patients and in seven patients in the non-irradiated group. No patient had signs of proctitis at rigid proctoscopy. The diameter of the anastomoses varied, but a proctoscope could be passed beyond the anastomosis in all patients. No further measurements of the anastomosis were made. There was no statistically significant correlation between anastomotic height and prevalence of anal incontinence.

MRP and MSP were significantly lower in the irradiated group compared with the surgery alone group (Figure 9). When filling a balloon in the rectum with air, the volume for FSF and the MTV did not significantly differ between the two groups (Table 13). The rectoanal inhibitory reflex was absent in four patients in the irradiated group and in three patients in the surgery alone group.

Patients reporting fecal incontinence had significantly lower MRP, MSP, and MTV compared to patients without anal incontinence (Figure 9 & Table 14).

**Figure 9.** Anorectal manometry findings in patients treated with and without preoperative RT and in continent & incontinent patients

**Table 13.** Anorectal manometry findings in patients treated with and without preoperative radiotherapy

	<b>pRT(+)</b> n=21	<b>pRT(-)</b> n=39	<b><i>p</i>-value</b>
FSF (mean mL)	57	51	0.34
MTV (mean mL)	105	97	0.26

**Table 14.** Anorectal manometry findings in continent & incontinent patients.

	<b>Fecal incontinence</b> n=23	<b>No fecal incontinence</b> (n=37)	<b><i>p</i>-value</b>
FSF (mean mL)	51	54	0.73
MTV (mean mL)	121	156	0.05

Two female patients in the irradiated group and one male patient in the non-irradiated group had an anterior sphincter defect at EUS. All three patients had anal incontinence. Scarring of the anal sphincters was identified in seven patients (33 %) in the irradiated group and in five patients (13 %) in the non-irradiated group ( $p=0.03$ ). Eleven of the twelve patients had varying degrees of anal incontinence.



## 5.4 ANORECTAL FUNCTION AFTER TME-SURGERY

Fecal incontinence was more frequent in TME-patients after pRT than after surgery alone (Table 15). More patients reported incontinence to gas, soiling and more frequent bowel movements in the irradiated group, but this difference was not statistically significant (Table 15).

**Table 15.** Anorectal function in patients operated with TME-technique.

	pRT(+) (n=45)	pRT(-) (n=23)	<i>p</i> -value
Fecal incontinence	29 (64%)	8 (35%)	0.02
Gas incontinence	32 (67%)	14 (58%)	0.60
Soiling	17 (39%)	4 (19%)	0.16
Stool frequency / week (range)	17 (4-50)	12 (3-50)	0.07

There were no significant differences in anorectal function between male and female patients, nor were there any significant differences in age between continent and incontinent patients. There was no statistically significant difference in anastomotic height between continent and incontinent patients. However, the three patients with an anastomotic level below 5 cm had various degrees of anal incontinence or soiling. Two patients in the TME(-) group and nine patients in the TME(+) group had experienced anastomotic dehiscence requiring surgery in the postoperative period. More irradiated patients had had anastomotic dehiscence, however this difference was not statistically significant. Eighty-two percent of patients with anastomotic dehiscence had fecal incontinence compared to 42% in the group without anastomotic dehiscence. There was a statistically significant correlation between anastomotic dehiscence and fecal incontinence ( $p=0.023$ ).

Patients operated with the TME technique had more frequently fecal incontinence than patients operated with non-TME techniques. There were no significant differences in frequency of fecal incontinence between non-irradiated TME(+) and TME(-) patients, but there was a trend in the same direction. In a logistic regression model, including pRT, TME surgery and anastomotic dehiscence, only pRT significantly increased the risk for anal incontinence. In the model the relative risk for anal incontinence was adjusted for the change in risk by the other two potential risk factors (Table 16).

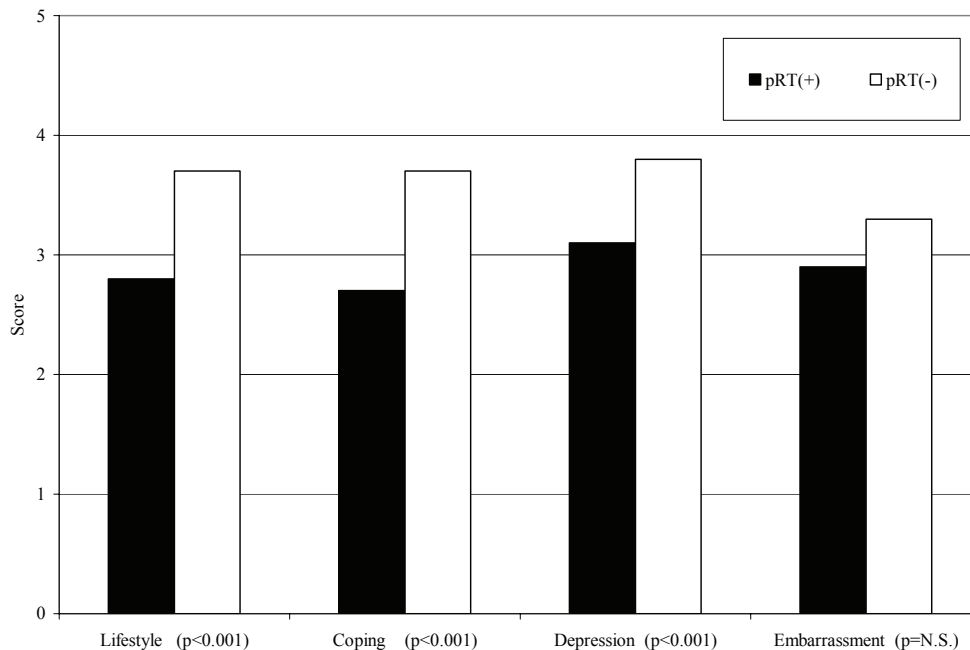
**Table 16.** Logistic regression analysis of the potential impact of pRT, TME-technique and anastomotic dehiscence on the long-term risk of developing anal incontinence.

	Relative Risk	95% C.I.	<i>p</i> -value
pRT(+)	2.78	1.23-6.29	0.01
TME(+)	1.49	0.67-3.32	0.33
Anastomotic dehiscence	3.79	0.45-32.19	0.22

Relative risk for anal incontinence for each risk factor is adjusted with linear regression for the other two variables.

In TME patients, the fecal incontinence QoL scale showed significantly worse scores in irradiated patients compared to non-irradiated patients in 3 out of the 4 scales in the questionnaire (Figure 10).

**Figure 10.** Fecal Incontinence Quality of Life in TME-patients treated with preoperative radiotherapy or surgery alone.



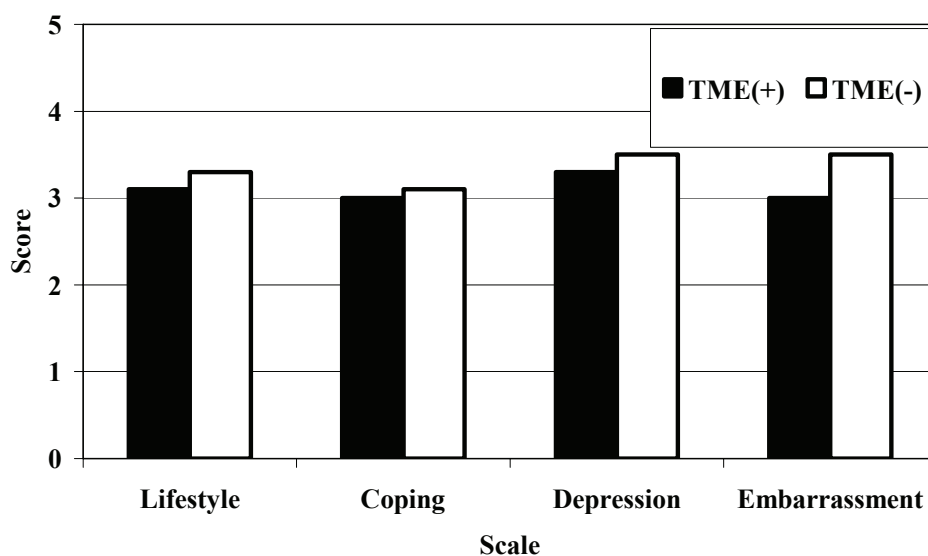
There was no statistically significant difference in any of the QoL-scales between patients operated with TME technique and non-TME technique (Figure 11).

In TME patients, mean anastomotic height measured from the anal verge was 6.5 cm. Mean anastomotic height was 6 (range, 3-9) cm in the irradiated group and 7.5 (range 3-12) cm in the non-irradiated group ( $p=0.014$ ). The diameter of the anastomoses varied, but a proctoscope could be passed beyond the anastomosis in all patients. No patient had signs of proctitis and no local recurrence was diagnosed.

The mean anastomotic height was higher in patients operated with non-TME technique than in patients operated with TME technique (9 cm vs. 6.5 cm;  $p<0.0001$ ).

In TME patients, MRP was significantly lower in irradiated patients than in non-irradiated patients and there was a trend towards lower MSP in the irradiated group (Table 17). FSF and the MTV did not significantly differ between the groups. The RAIR was absent in nine patients in the irradiated group and in two patients in the non-irradiated group.

**Figure 11.** Fecal Incontinence Quality of Life in TME and non-TME patients.



**Table 17.** Anorectal manometry in patients operated with TME technique.

	pRT(+) (n=30)	pRT(-) (n=14)	<i>p</i> -value
MRP (mmHg)	26	39	<0.01
MSP (mmHg)	69	81	0.34
FSF (mL)	62	65	0.81
MTV (mL)	131	145	0.53

MRP and MSP were significantly lower in patients operated with TME technique than in patients operated with non-TME technique (Table 18).

**Table 18.** Anorectal manometry in patients operated and not operated with TME.

	TME(+) (n=44)	TME(-) (n=64)	<i>p</i> -value
MRP (mmHg)	30	40	0.01
MSP (mmHg)	73	110	<0.01
FSF (mL)	63	52	0.10
MTV (mL)	136	143	0.58

In non-irradiated patients, MSP and FSF were significantly lower in the TME(+)-group and there was a trend that MRP was also lower (Table 19).

**Table 19.** Anorectal manometry in non-irradiated patients.

	<b>TME(+)</b> (n=14)	<b>TME(-)</b> (n=39)	<b><i>p</i>-value</b>
MRP (mmHg)	39	62	0.195
MSP (mmHg)	81	143	0.042
FSF (mL)	65	51	0.020
MTV (mL)	145	150	0.742
RAIR (present / not present)	12 / 2	36 / 3	0.599

## 6 DISCUSSION

### 6.1 PREOPERATIVE STAGING (PAPER I)

Preoperative staging is an essential part in planning the optimal treatment for rectal cancer. Several methods can be used. Rectal palpation is used for judging accessibility, location and mobility. Endorectal ultrasonography, CT and MRI can then be used according to local practice and availability. ERUS has a high accuracy in evaluation of bowel wall penetration, especially in early cancers and benign lesions. CT and MRI may have higher accuracy in assessment of regional lymph node metastasis (Schaffzin *et al.*, 2004). For visualization of the CRM, MRI is superior to ERUS (Beets-Tan *et al.*, 2004).

Paper I demonstrates that ERUS is a useful tool in the assessment of patients with rectal tumors. ERUS was reliable in assessing the grade of tumor infiltration into the bowel wall, while spread to mesorectal lymph nodes was less accurately assessed. The overall accuracy in detecting depth of wall penetration was 69 %, while 18 % of the tumors were overstaged and 13 % understaged. In previous studies, the accuracy ranged between 61 and 94 % (Table 2). These studies were however mostly limited in size compared with the present study.

In a previous study (Orrom *et al.*, 1990), from the University of Minnesota, a higher accuracy (75 %) was reported and improved accuracy with more experience was anticipated. The present larger study contradicts this statement. When analyzing the results over time, we could not see any trends that the accuracy improved with time. Experience is however important for adequate interpretation of ERUS images. All investigations in the present study were performed by one of four colorectal surgeons experienced in the technique. Thus, the present study demonstrates that even experienced ultrasonographers staged tumors incorrectly when compared with the pathoanatomical examination. Large and stenotic tumors are difficult or even impossible to image with ERUS. In the present series 37 of the examinations (3 %) had to be excluded due to inconclusive results.

Due to irregular tumor surface and variations in the rectal lumen, the muscularis propria is not always possible to image circumferentially. This is essential for distinguishing between uT2 and uT3 tumors.

Three-dimensional ultrasonography has recently been implemented as a new diagnostic tool. The 3D-image might facilitate the understanding of the spatial relations between structures on the pictures. This technique is still under evaluation (Schaffzin *et al.*, 2004).

The MRI-technique is currently undergoing rapid development. The implementation of pelvic phased-array coils result in images distinguishing between the different bowel layers (Brown and Daniels, 2005). The accuracy for T-staging in the present study is similar to previous reports using MRI (Schaffzin *et al.*, 2004). MRI is not as operator dependant as ERUS, but the technique is time consuming and more expensive. CT can not distinguish between the different layers within the bowel wall. CT can therefore only differentiate between tumors confined to the bowel wall (T0/T1/T2) and tumors extending through the bowel wall (T3/T4).

Assessment of tumors penetrating into neighboring pelvic structures is sometimes difficult with the limited range of ERUS. MRI is frequently used for this assessment

with good accuracy (Blomqvist *et al.*, 2002). In the present study only six pT4 tumors were included, making general conclusions on these tumors uncertain.

In the present study, 18 % of the tumors were overstaged at ERUS and the tumors were less advanced than the preoperative ERUS had indicated. These patients were at risk for over treatment. Reasons for over staging might be peritumoral inflammation, causing the tumor to appear more advanced on the ERUS images. Another reason might be examiner bias in order to avoid under staging.

Understaged patients were at risk of receiving suboptimal treatment. If the postoperative pathoanatomical examination showed an advanced tumor understaged with ERUS, the patient could still receive adjuvant therapy postoperatively. One reason for under staging might be microinvasion of the tumor, which can be demonstrated under the microscope but is beyond the resolution of ultrasonography. Most patients with advanced tumors at ERUS (uT3, uT4 and/or uN1) were treated with preoperative chemoradiation and thus excluded from this study. Selection bias for these tumors can therefore not be excluded.

The perirectal nodal status was less accurately assessed by ERUS and this is in accordance with several previous reports (Table 3). In the present series, relatively few patients (n=56) with pathologic lymph nodes at ERUS (uN1) were included. The majority of patients with uN1 disease received preoperative chemoradiation therapy and they were thus excluded from the study.

Of the 238 patients treated with radical surgery, 182 had no involvement of the mesorectal lymph nodes on ERUS. This was correct in 124 patients (68 %). Forty of the 58 patients with false negative N-staging had uT3-uT4 tumors. In previous reports, MRI has demonstrated similar accuracy for detecting spread to perirectal lymph nodes, (Blomqvist *et al.*, 2000) while CT has similar or lower accuracy (Koh *et al.*, 2006).

PET-CT and other new imaging techniques might improve accuracy for detecting lymph nodes. However, all imaging techniques require that tumor spread lead to change in characteristics, i.e. change in the shape, echogenicity, or size. If a lymph node contains only small metastatic growth, it will probably not be detected by any of the present imaging modalities. This might in part explain the low sensitivity by ERUS, CT and MRI in detecting local lymph node involvement. False positive uN1 is sometimes explained by reactive, inflammatory changes in the lymph node. The inflammation causes change in shape and echogenicity that might imitate metastatic involvement. PET-CT might be helpful to differentiate between reactive lymph node enlargement and lymph nodes with metastatic growth (Koh *et al.*, 2006).

Of patients undergoing radical surgery, ERUS staged 73 tumors as benign or as an early cancer (uT0N0, uT1N0 or uT2N0). These tumors were potential candidates for local treatment. Fifty-three of these 73 patients (73 %) had benign or an early cancer at the postoperative pathoanatomical examination. Of the 20 patients with tumors unsuitable for local treatment (pT3/pT4 or pN1), 17 had been classified as uT2N0 two as uT1N0 and one as uT0uN0. Tumors classified as uT2 tumors thus run a significant risk of being more advanced than demonstrated on ERUS. It is noteworthy that a previous report from the University of Minnesota reported a high local recurrence rate was found after local excision of T1 and T2 tumors (Mellgren *et al.*, 2000). The results in the present study indicate that uT2uN0 tumors may be understaged and possibly not suitable for local excision.

### *Conclusions preoperative staging of rectal tumors*

For local staging of benign rectal tumors and early rectal cancer, ERUS is an accurate method. For evaluation of the mesorectal fascia and the CRM MRI with pelvic phased-array coils is currently the most reliable tool. For invasion into neighboring organs spiral CT and MRI have comparable accuracy. For detection of local lymph nodes, ERUS and MRI are comparable. PET-CT might be an option for N-staging. CT has the advantage of being able to detect distant metastases in remote organs with a single scan, but the resolution is not enough for T-staging of rectal tumors.

## **6.2 LONG-TERM MORBIDITY AFTER PREOPERATIVE RADIOTHERAPY AND SURGERY FOR RECTAL CANCER (PAPER II-IV)**

Paper II demonstrates that rectal cancer patients treated with pRT have an increased risk of complications at long-term FU when compared to patients treated with surgery alone. Cardiovascular disease was statistically significantly more common in irradiated patients compared to non-irradiated patients. Irradiated patients also reported urinary incontinence, diarrhea and anal incontinence more often than non-irradiated patients.

Anal incontinence (Papers III and IV) was common both after AR and LAR with old surgical technique and after LAR with TME-technique. More patients treated with TME-surgery had anal incontinence compared with patients treated with old technique. In a multivariate analysis, however, only pRT increased the risk of anal incontinence at FU. At anorectal manometry, irradiated patients treated with AR or LAR also had lower intra anal pressures.

The findings in the present studies (Paper II-IV) are in line with some previous reports (Varma *et al.*, 1986, Williamson *et al.*, 1994, Frykholm-Jansson *et al.*, 1996, Holm *et al.*, 1996, Dahlberg *et al.*, 1998, Martling *et al.*, 2001, Dehni *et al.*, 2002, Marijnen *et al.*, 2002, Nesbakken *et al.*, 2002, Amman *et al.*, 2003, Rasmussen *et al.*, 2003, van Duijvendijk *et al.*, 2003, Birgisson *et al.*, 2005). However, the results in the present studies need to be interpreted with some caution because of the retrospective nature of the studies. Of the originally more than 1400 patients in the Stockholm I and II trials and more than 260 patients in the Stockholm TME-study, only 207 were available for FU. A majority of the patients (1 298 patients) had diseased during the FU-period, but almost 170 patients had to be excluded for different reasons (Unable to attend a FU-visit because of physical or mental limitations, had moved outside the Stockholm area or not willing to participate.) We do believe, however, that it is hard to achieve a higher response rate at long-term FU. These numbers demonstrate the difficulties in performing a long-term FU study in an aged population. Hence, the limited number of patients in each group available for assessment may cause problems with selection bias and difficulties to detect true differences.

In the present study each type of complication, except for venous thrombo-embolism, was more common in irradiated patients than in non-irradiated patients. Only three (cardiovascular disease, urinary incontinence and anal incontinence) out of eight complications were however significantly more common in the irradiated group.



### *Long-term complications of preoperative radiotherapy in relation to radiotherapy technique*

Late adverse effects from radiation therapy are dependent upon the radiation dose and the irradiated volumes of organs at risk. The irradiated volume in pRT for rectal cancer has gradually decreased during the last decades. Thus, using the same radiation schedule, 5 x 5 Gy in one week, it can be anticipated that patients treated more recently are at less risk for late adverse effects than those included in the Stockholm trials.

The irradiated volumes in the Stockholm trials, particularly in Stockholm I, but also in Stockholm II were larger than those in the other Swedish trials using 5 x 5 Gy run in parallel, the Uppsala trial (Frykholm-Jansson *et al.*, 1993) and the SRCT (Anonymous V, 1997). The Stockholm II trial and the SRCT were overlapping, however, the radiation technique was simplified in Stockholm compared to the rest of Sweden, and what is presently recommended. This difference in radiation technique may have resulted in a greater radiation burden to surrounding normal tissues.

Since the irradiated volume was much larger in Stockholm I (from the L2 vertebra to below the anal verge, anterior-posterior beams, thus resulting in inclusion of the entire urinary bladder and a large small bowel volume) than in Stockholm II (from the L4 vertebra to below the anal verge, 4 beams, no shields), it could be suspected that less late morbidity would be seen in Stockholm II, but this was not the case (see Table 9). Besides small patient numbers, the groups may, due to the design of this FU study, not be comparable (Stockholm I patients younger when irradiated, older at investigation, longer delay from primary treatment to the interview, greater drop-out), precluding firm conclusions. When a similar FU study was done after 5 and 10 years in the Uppsala trial (individualized lower border, upper level L3, 3 beams, individualized shields), run in parallel to Stockholm I, it was not possible to detect any increase in late morbidity in preoperatively irradiated patients (Frykholm-Jansson *et al.*, 1993). Again, limited patient numbers together with the fact that it is notoriously difficult to compare results from different trials make firm conclusions difficult.

The acute toxicity was much less in the Uppsala trial than in the Stockholm I trial (Pahlman *et al.*, 1990), and it is thus reasonable to anticipate less late toxicity as well, since both acute and late toxicity are dependent upon irradiated volumes, although the relations may differ. Due to a lower radiation burden for patients treated within the SRCT outside of Stockholm (shielding of tissues not at risk containing tumor cells were prescribed) than for those from Stockholm participating in Stockholm II, less late toxicity could be anticipated in patients treated outside Stockholm.

Some increase in late toxicity was also seen after five years of FU in Stockholm II (Holm *et al.*, 1996), whereas this could not be detected after eight years of FU in the SRCT (Dahlberg *et al.*, 1999). Some late toxicity with impaired bowel and sexual function has been reported from the Dutch TME trial (Marijnen *et al.*, 2005). In the Dutch TME trial, the lower border was individualized, 3 or 4 beams were used, and the upper border was at the L5 vertebra. Thus, less late toxicity could be anticipated, but this requires much longer FU. In the Dutch TME trial, the radiation treatment was not individually planned. Individual dose planning has the potential to further reduce the volumes outside the tumor target receiving the same dose as the prescribed tumor dose. Individual dose planning, conforming the radiation beams is much more readily



performed today than in the past (Johansson *et al.*, 2003). The extent to which this technical development reduces late morbidity can only be known after long-term FU of large patient groups.

### *Cardiovascular complications*

An increased incidence of cardiovascular mortality was observed in irradiated patients in the Stockholm I trial (Anonymous II, 1990). The age limit for inclusion in the Stockholm II study was therefore set to 80 years and the irradiated volume was smaller. No statistically significant increased mortality after RT was seen in the Stockholm II trial. However, the majority of patients in the present study were recruited from the Stockholm II trial and we found a significantly increased prevalence of cardiovascular disease in irradiated patients. This finding is important, but the mechanisms remain unclear. Several possibilities have previously been suggested. Irradiation of the pelvis can cause an inflammatory response in the pelvic arteries (Baerlocher *et al.*, 2004) and an increased secretion of growth factors into the blood stream may accelerate the atherosclerotic process also in remote arteries. The number of patients with claudicatio, indicating atherosclerosis in the pelvic / femoral arteries, was too small to disclose any significant difference between irradiated and non-irradiated patients.

### *Urinary dysfunction*

Urinary incontinence was common in both irradiated and non-irradiated patients, but this symptom was significantly more common in irradiated patients. Surgical damage to autonomic nerves inhibits sphincter function and this may be an important reason for the high frequency in both groups. Radiation therapy may cause fibrosis in the bladder, the urethral sphincters and their nerves and may lead to an increased risk for urinary incontinence in irradiated patients (Grise *et al.*, 2001). Backward displacement of the bladder after APR may be a reason for incomplete bladder emptying. In the present study, however, no statistically significant differences in urinary incontinence or difficulties in bladder emptying were found between patients operated on with AR vs. APR. We therefore conclude that the radiation therapy *per se* may increase the risk of urinary incontinence. In a study by Chatwin *et al.*, (2002), seven percent of patients had urinary incontinence after AR compared to 33 % in the present study. The mean age in the present study was higher than in the study by Chatwin and this may be an explanation for the higher prevalence of urinary incontinence in the present study (Paper II). New surgical techniques with nerve sparing dissection, introduced after the Stockholm I and II trials, may also explain a lower incidence of urinary incontinence in more recent studies (Maas *et al.*, 1998). Urinary incontinence is more common with increasing age, but as the irradiated and non-irradiated patients were well balanced with regard to age and gender, the increased morbidity after pRT is unlikely to be the result of skewed age and sex distribution.

## *Gastrointestinal complications*

Irradiated patients had more diarrhea symptoms than non-irradiated patients. As no signs of proctitis were found at rigid proctoscopy in the patients with anorectal continuity, this should not be the reason for these symptoms. Irradiation of the small bowel can cause malabsorption (Bismar *et al.*, 2002) and thus diarrhea and this may be one explanation for the difference between the groups. The higher prevalence of diarrhea after pRT may also partly explain the higher frequency of fecal incontinence in irradiated patients treated with AR.

In a previous FU of patients included in the Stockholm I trial an increased incidence of small bowel obstruction in irradiated patients was found (Holm *et al.*, 1996). This was not found in the Stockholm II trial. The discrepancy may be because of the smaller irradiated volume in Stockholm II (Martling *et al.*, 2001). In the present study, the majority of patients were recruited from the Stockholm II trial. This and the small patient population may explain why the difference in small bowel obstruction between irradiated and non-irradiated patients was not statistically significant in the present study. In a recent FU of patients in the Swedish Rectal Cancer study by Birgisson *et al.* (2005) more irradiated patients had been admitted to hospital for gastrointestinal disorders, e.g. small bowel obstruction, abdominal pain and nausea.

## *Anorectal dysfunction*

In Paper III we found that irradiated patients had significantly more anal incontinence and worse anorectal function compared with patients treated with surgery alone. Our findings are supported by several previous studies reporting impaired anorectal function in patients treated with AR or LAR (Dahlberg *et al.*, 1998, Ammann *et al.*, 2003). The functional outcome after AR and pRT has previously been studied by Dahlberg *et al.* (1998) using questionnaires; they found an increased incidence of anal incontinence after pRT when compared with surgery alone. The study by Dahlberg was a FU of patients operated within the SRCT. At mean FU of 80 months 50% of the 84 irradiated patients had incontinence to solid feces compared with 24% of 87 patients treated with surgery alone. These figures resemble the findings in the present investigation.

Paper IV demonstrates that anorectal dysfunction is common after LAR with TME-technique for rectal cancer at long-term FU, especially if pRT is used. These findings are in line with some previous experience in the literature. In a prospective study from the Netherlands, van Duijvendijk *et al.* (2002) found impaired anorectal function after TME surgery, especially after pRT at FU after one year. The Dutch Colorectal Cancer Group has also reported impaired anorectal function at long-term FU after pRT in conjunction with TME-surgery (Peeters *et al.*, 2005). However, in another study, Nesbakken *et al.* (2002) did not find any significant differences in anal incontinence when comparing patients with high and low rectal anastomoses. However, rectal compliance was compromised after surgery in both groups. In the present study, the number of TME-patients treated with surgery alone was limited, but despite this limitation, anorectal dysfunction was more common after both TME-

surgery and radiation several years after treatment. The logistic regression analyze showed a significantly increased risk for anal incontinence in the pRT(+) group. TME-surgery and anastomotic dehiscence did not influence the risk significantly. This finding implies that pRT is an independent risk factor for developing anal incontinence after AR.

The pathophysiologic reasons for development of the so-called LAR-syndrome, i.e., clustering, anal incontinence, and soiling, remain unclear. Different mechanisms have been suggested, including decreased rectal capacity, decreased MRP, and failure of the rectoanal inhibitory reflex (van Duijendijk *et al.*, 2002). RT has been postulated to cause damage to the myenteric plexus in the internal anal sphincter and thus impaired resting pressure in the anal canal (Varma *et al.*, 1986). It is possible that the 5x5 Gy pRT used in the Stockholm trials causes fibrosis and impaired impulse conduction in sacral nerves and fibrosis in the anal sphincters (Dahlberg *et al.*, 1998).

All patients in the present study who were treated with pRT had the anal sphincters included in the radiation field. Fibrosis of the sphincter may therefore partially explain the lower MRP and MSP in patients treated with pRT as also reported by Ammann *et al.* (2003). Fibrosis of the pudendal nerves as a result of RT might also diminish the anal pressures. There is not always a straightforward relationship between anorectal manometry pressure curves and anal continence. In the present study, however, incontinent patients had significantly lower MRP compared with continent patients. Leaving some of the irradiated rectum behind and stapling of an anastomosis could possibly result in impaired rectal compliance. However, we did not find any difference in MTV between irradiated and non-irradiated patients. In a study by Amin *et al.* (2003) on functional outcome after colonic pouch-anal anastomosis, no negative effect from preoperative radiation was found. These findings may support the opinion that it is preferable to make a colonic pouch anal anastomosis than to leave an irradiated rectal remnant for a colorectal anastomosis.

Patients treated with TME-surgery, but no radiation, had significantly lower MSP in the anal canal compared with patients treated with non-TME technique without radiation. There was no significant difference in resting pressure, but there was a trend that TME patients had lower MRP as well. Sphincter injuries can occur during TME surgery, during the dissection or the stapling of a low rectal anastomosis (Matzel *et al.*, 2003).

Significantly more patients in the irradiated group Paper III had scarring of the anal sphincters at EAUS. Irradiation of the sphincters is a possible reason for these defects. Eleven of 12 patients with scarring of the anal sphincters at EAUS also had anal incontinence. Trauma to the anal sphincters by the circular stapling device is another possible explanation of the scarring; however, this does not explain the difference between irradiated and non-irradiated patients. Thus, radiation-induced scarring of the anal sphincters might contribute to anal incontinence and decreased MRP in irradiated patients. The exclusion of the anus from the radiation field in patients with cancers in the mid and upper third of the rectum, scheduled for AR, may diminish the negative influence of pRT on bowel function.

In a randomized trial between straight and colonic J-pouch anastomoses by Hallböök, *et al.* (1996) J-pouch anastomosis was associated with better bowel function than a straight anastomosis. Most patients treated with old surgical technique had end-to-end anastomosis which might contribute to the poor long-term anorectal function. However conflicting results exist. In a randomized study comparing end to side and J-

pouch anastomoses after TME-surgery by Machado *et al.* (2003) no differences in anorectal function were found at short-term (12 months) FU. Patients treated with TME-surgery in Paper IV had both end to end, end to side and colonic J-pouch anastomoses performed. The limited numbers of patients in each group make conclusions on functional outcome after different types of anastomoses difficult.

Anorectal function often deteriorates with increasing age and this might be one reason for the large proportion of incontinent patients in the present older study population. However, this should affect both groups equally because both groups in the present study were of the same mean age. Patients frequently reported a gradual improvement of anal incontinence the first years after surgery, but symptoms thereafter were rather stable. At long-term FU many of the patients had accepted their impaired anorectal function and had learned to live with their incontinence.

The distance from the anal verge to the anastomosis was mean nine cm in patients operated with old technique and there was no difference in the anastomotic height between irradiated and non-irradiated patients. There was no statistically significant correlation between anastomotic height and prevalence of anal incontinence. Most patients had anastomosis around ten cm from the anal verge; thus, few patients had very low anastomosis. As could be expected, patients treated with TME-technique had lower anastomoses compared to patients treated with non-TME-technique had (6.5 cm and 9 cm from the anal verge respectively). Patients with a low colorectal anastomosis are considered to be at a higher risk for developing anal incontinence and this may contribute to the higher incidence of fecal incontinence in patients operated with TME surgery. More patients with low anastomosis had anal incontinence compared to patients with high anastomoses however this difference was not statistically significant.

### *Other complications*

At rigid proctoscopy no patient had signs of proctitis or local recurrence, as was expected at long-term FU. Local recurrence after more than nine years after surgery for rectal cancer is an unlikely event and was not found in any patient.

No patient had signs of a manifest cancer of other organs in the pelvis. Irradiation of the prostate in prostate cancer has been associated with a significantly increased risk for rectal cancer at long-term FU (Baxter *et al.*, 2005). Birgisson found an increased number of tumors in irradiated patients at FU of the SRCT (Birgisson *et al.*, 2005). Thus pelvic irradiation may increase the risk for secondary cancers. We could not verify that in the present studies. One reason for this may be the limited number of patients in the present study.

Late onset proctitis after pelvic radiation has been reported to occur in approximately 2-10 % of patients by Vyas *et al.*, (2006). Chronic proctitis may be severe and handicapping complication to pRT, however, no patient in the present FU had signs of this complication at proctoscopy.

In the present study (Paper II) there was no difference in incidence of hip and pelvic fractures between irradiated and non-irradiated patients. In a previous FU of patients in the Stockholm I and II trials (Holm *et al.*, 1996), irradiated patients had significantly more fractures. However this difference was only seen in the first three postoperative years. Our findings are therefore in line with this previous report.

Patients in the irradiated group reported significantly more pain ( $p=0.049$ ) compared to non-irradiated patients, however no such trend was seen for pain in the pelvic area.

### *Quality of life*

QoL analysis in Paper II demonstrated minor differences between patients treated with AR compared to those treated with APR. APR-patients scored significantly lower on physical function scale. Some previous studies evaluating QoL assessment in rectal cancer have demonstrated that patients with a colostomy have a lower QoL score (Sprangers *et al.*, 1995). However conflicting results exist. Rauch *et al.* (2004) reported that patients with a colostomy had better QoL scores than patients treated with AR. The patients in the present study had had a long time to adapt to a colostomy which may explain our findings. In addition, patients may consider a colostomy to be a limited price for being cured from a malignant disease.

We found QoL differences between irradiated and non-irradiated patients, irradiated patients scored significantly lower on the social function scale. In a recent FU of patients treated with TME-surgery with or without pRT, Marijnen *et al.* (2005) also found small differences in QoL between irradiated and non-irradiated patients. In their study, colostomy patients scored higher on physical and psychological dimensions than AR patients.

As no preoperative QoL investigations were performed, the QoL scores in our study (Paper II) were compared to a normal material sampled from the Swedish population (Michelson *et al.*, 2000) (Table 10). Only minor differences were found between the study population and the Swedish sample. However, no statistical comparisons could be made, since only mean values were available from the Swedish sample.

Comparisons of scores between male and female patients are detailed in Table 11. Female patients scored significantly lower on global health score, and in three additional function scores. Also on the symptom scores female scored worse than male patients on constipation, fatigue, pain and insomnia scales. These findings are in line with other investigations. Schmidt *et al.* (2005) reported significantly lower global health and physical functioning scores in female patients. Female patients also had higher symptom scores on the fatigue scale in their five-year FU.

The impact of anal incontinence on daily life was evaluated with a standardized questionnaire (Rockwood *et al.*, 2000). As could be anticipated, the QoL scores were significantly lower in incontinent vs. continent patients in all four scales used in the questionnaire. To our knowledge this questionnaire has not been frequently used previously in rectal cancer patients. The lower QoL scoring in the incontinent group indicates a need for improved FU and treatment of anal incontinence after AR for rectal cancer. Although conservative treatment is effective for many patients, some patients probably would benefit from additional treatment for their anal incontinence. In a pilot study, Matzel *et al.* (2002) reported promising results using sacral nerve stimulation in three patients with anal incontinence after LAR for rectal cancer.

In a recent Norwegian study, an impaired anorectal function was also found in irradiated patients, although the QoL was not affected by the incontinence symptoms (Guren *et al.*, 2005). In the Norwegian study, the QLQ-C30 and QLQ-CR38

questionnaires were used, but no QoL instrument focusing on anal incontinence. This might be a reason for the discrepancy in impact on QoL in the present study and the Norwegian study. In a recent study from Italy (Urso *et al.*, 2006), 44 patients with locally advanced rectal cancer were prospectively assessed with QoL questionnaire EORTC QLQ-CR38, QoL dropped after preoperative chemoradiation and did not improve during their eight-month FU.



## 7 CONCLUSIONS

Aims are repeated along with the conclusions for the readers' convenience.

Aims	Conclusions
1. Review a single institution experience with endorectal ultrasonography (ERUS) and to determine its accuracy in discriminating between early and advanced rectal tumors.	ERUS is useful in staging rectal tumors preoperatively. It identifies transmural invasion and reliably distinguishes between invasive and non-invasive tumors. Our data indicate that the accuracy of ERUS in preoperative staging of rectal tumors varies by tumor stage.
2. Assess if ERUS is useful for selection of patients for preoperative radiotherapy (pRT) and local treatment.	ERUS is a reliable method to determine the depth of invasion into the bowel wall and is thus useful for selection of patients for pRT and local treatment.
3. Assess long-term morbidity and quality of life (QoL) in patients undergoing rectal cancer surgery with or without pRT.	pRT in rectal cancer increases the incidence of urinary dysfunction and may increase the risk of cardiovascular morbidity at long-term follow-up. This increased morbidity does not influence global QoL.
4. Assess late effects on anorectal function of anterior resection (AR) for rectal cancer with or without pRT.	pRT in rectal cancer impairs anorectal function after AR and increases anal incontinence at long-term follow-up. About one-half of irradiated patients have fecal incontinence at long-term follow-up. Fecal incontinence impairs QoL.
5. Compare anorectal function at long-term follow-up in patients treated with low anterior resection (LAR) with TME-surgery (Total Mesorectal Excision) or traditional AR with or without pRT.	LAR for rectal cancer significantly impairs anorectal function at long-term follow-up, especially if pRT is used. TME-technique does not impair anorectal function more than old technique. Preoperative radiotherapy worsens the quality of life in patients operated with TME-technique due to their impaired anorectal function.

Preoperative radiotherapy in rectal cancer surgery improves local control and survival but these positive effects need to be balanced against the long-term side effects.

A reliable preoperative staging is an essential part of modern rectal cancer management, for selection of patients that can benefit from preoperative radiotherapy, and for tailoring the optimal surgical treatment.





## 8 SUMMARY IN SWEDISH

### Bakgrund

Ändtarmscancer är en av våra vanligaste cancersjukdomar. Varje år drabbas ca 3 000 svenskar av sjukdomen. Femårsöverlevnaden har de senaste åren förbättrats och är nu ca 70%. Kirurgisk behandling är grundstommen i behandlingen, men kan kompletteras med strålbehandling och/eller cytostatikabehandling.

### Preoperativ stadiindelning av ändtarmstumörer

En korrekt stadiindelning av tumörer i ändtarmen är viktig för att kunna avgöra om strålbehandling behövs före operation (preoperativt). Stadiindelningen kan göras med ultraljud (ERUS), magnetkamera eller skiktröntgen. Information om tumörens stadium är också värdefullt för planering av kirurgin. Ultraljud via analkanalen (ERUS) är en metod som ofta används för stadiindelning före operation. Erfarenheten av ERUS är begränsad vid vår institution. Vid University of Minnesota finns emellertid en omfattande erfarenhet och vi har därför retrospektivt analyserat ett stort material därifrån för att utvärdera ERUS tillförlitlighet för preoperativ stadiindelning.

### Preoperativ strålbehandling

Mellan 1980 och 1993 genomfördes två prospektiva randomiserade studier om värdet av preoperativ strålbehandling vid ändtarmscancer i Stockholmsregionen (Stockholm I & II). Totalt ingick 1406 patienter i studierna. Patienterna randomiserades till enbart kirurgi eller till strålbehandling följt av kirurgi. Stockholmsstudierna innebar att man för första gången gav strålbehandlingen under en kort tid (en vecka) istället för i mindre fraktioner under längre tid (4-6 veckor). Studierna visade en halvering av antalet återfall av sjukdomen i lilla bäcken hos de patienter som strålbehandlats och i den senare studien registrerades även en minskad dödlighet i ändtarmscancer hos strålade patienter. Med stöd från dessa studier och från andra strålbehandlingsstudier, behandlas nu en majoritet av patienterna med ändtarmscancer i Sverige med preoperativ strålbehandling.

Biverkningar efter preoperativ strålbehandling av ändtarmscancer har tidigare studerats, dock med begränsad uppföljningstid. Kunskapen om bieffekter på lång sikt är begränsad. Det är känt att strålbehandling kan ge en ökad risk för hjärtsjukdomar, tarmvred och frakturer i höft och bäcken. Fördjupad kunskap om strålbehandlingens effekter är viktigt att väga in vid beslut om att ge strålbehandling.

### TME-teknik vid kirurgi av ändtarmscancer

Operation av ändtarmscancer innebär att hela eller delar av ändtarmen bortopereras. Vid tumörer nära ändtarmsöppningen tages hela ändtarmen och ändtarmsöppningen bort och patienten får en permanent stomi (APR). Vid tumörer längre upp i ändtarmen kan en del av ändtarmen och ändtarmsöppningen sparas och tjocktarmen kopplas ner till ändtarmsresten (AR).

TME-teknik innebär att ändtarmen mobiliseras med diatermi eller sax under ögats kontroll. Dissektionen fortsätter ner till bäckenbotten och ändtarmen borttages ner till bäckenbotten. Tjocktarmen kopplas sedan till ändtarmsresten. Detta medför reducerad reservoarfunktion i ändtarmen. Tekniken innebär också dissektion på korsbenets framsida, med risk för skador på nerver viktiga för bland annat urinblåsefunktion och

tarmtömningsfunktion. Hur tarmtömningsfunktionen påverkas jämfört med tidigare använd kirurgisk teknik är oklart. Med äldre teknik friades ändtarmen ofta med trubbig fingerdissektion utan ögats kontroll.

TME-tekniken infördes i Sverige i början av 90-talet och har, i kombination med preoperativ strålbehandling visats kunna medföra reducerad förekomst av återfall i lilla bäckenet från ca 15 % till 6 %. Andelen patienter som behöver permanent stomi har också minskat.

Patienter inkluderade i Stockholm I & II studierna är opererade med äldre teknik. I Stockholm infördes TME-teknik med en utbildningsinsats för Kirurger i länet med flera workshops och inom ramen för studier med standardiserade protokoll och uppföljning. Data på patienter opererade med TME-teknik 1995-96 i Stockholmsområdet finns insamlat i ett register.

TME-teknik i kombination med preoperativ strålbehandling kan potentiellt innebära en ökad risk för försämrad tarmtömningsfunktion, men få studier har evaluerat detta problem. Skillnader i tarmtömningsfunktion mellan patienter opererade med TME-teknik och med den äldre tekniken kan även ha betydelse för val av operationsmetod.

## Frågeställningar

1. Kan ERUS användas för att skilja mellan tidig och lokalt avancerad ändtarmscancer?
2. Är ERUS en användbar metod för att selektera patienter till preoperativ strålbehandling?
3. Innebär preoperativ strålbehandling ökad risk för senbiverkningar och påverkan på livskvaliteten vid långtidsuppföljning?
4. Innebär preoperativ strålbehandling en ökad risk för försämrad tarmtömningsfunktion?
5. Innebär TME-kirurgi en ökad risk för försämrad tarmtömningsfunktion?

## Studier

**Studie I:** Accuracy of endorectal ultrasonography in preoperative staging of rectal tumors

*Material & metod:* 545 patienter med ändtarmstumörer undersöktes med ERUS för stadiindelning. Efter operation jämfördes stadiindelningen från ultraljudsundersökningen med stadiindelning på operationspreparatet med mikroskopi.

*Resultat:* Korrekt stadiindelning med ultraljud avseende T-stadium (djupväxt i tarmväggen) uppnåddes i 69 %. 18 % av tumörerna skattades till ett för högt T-stadium. N-stadium (metastas i lymfkörtlar runt ändtarmen) skattades rätt i 64 %. ERUS kunde skilja mellan godartad tumör och cancer med >85 % säkerhet.

*Slutsatser:* ERUS är en användbar metod för att stadiindela rektala tumörer preoperativt och kan användas för att selektera patienter till preoperativ strålbehandling.

**Studie II:** Late adverse effects of short course preoperative radiotherapy in rectal cancer

*Material & metod:* Samtliga patienter från Stockholm I & II studierna kontaktades och ombads att delta i studien. 139 patienter svarade på frågeformulär inkluderande

sjukhistoria, urinblåsefunktion och livskvalitet. Patienterna kallades till ett läkarbesök där undersökning av buken och eventuell stomi utfördes.

*Resultat:* Patienter behandlade med preoperativ strålbehandling hade signifikant mer komplikationer än patienter behandlade med enbart kirurgi (69 vs. 43 %,  $p=0,002$ ). Signifikant skillnad i komplikationsfrekvens förelåg även avseende hjärt-kärlsjukdom (38 % vs. 21 %,  $p=0,03$ ) och urininkontinens (46 vs. 27 %,  $p=0,02$ ). Livskvalitetsmätning visade små skillnader mellan strålade och ostrålade patienter. Ingen skillnad fanns i förekomst av tunntarmsvred eller bäcken- och höftfrakturer.

*Slutsatser:* Preoperativ strålbehandling ökar risken för hjärt-kärlsjukdom och urininkontinens på lång sikt, men strålning påverkar inte total livskvalitet.

### **Studie III:** Long-term effect of preoperative radiation therapy on anorectal function

*Material & metod:* Patienter från Stockholm I & II studierna som opererats utan anläggande av permanent stomi kontaktades och ombads att delta i studien. 64 patienter svarade på frågeformulär inkluderande sjukhistoria, tarmfunktion och livskvalitetsformulär samt undersöktes med rektoskopi, (instrument för att titta in i tarmen), mätning av slutmuskelfunktionen (anorektal manometri) och med ultraljud av slutmuskeln.

*Resultat:* Patienter behandlade med preoperativ strålbehandling hade signifikant mer anal inkontinens (57 vs. 26 %,  $p=0,01$ ). Strålade patienter hade också fler tarmtömningar per vecka (20 vs. 10,  $p=0,02$ ). Vid undersökning med anorektal manometri hade strålade patienter signifikant lägre vilotryck (35 mmHg vs. 62 mmHg,  $p<0,001$ ) och lägre kniptryck (104 mmHg vs. 143 mmHg,  $p=0,05$ ). Fler patienter i den strålade gruppen hade ärrbildning i slutmuskeln synliga med ultraljud (33 % resp. 13 %  $p=0,03$ ). Patienter med anal inkontinens hade lägre livskvalitet.

*Slutsatser:* Anal inkontinens är vanligt efter operation av ändtarmscancer och förvärras av strålbehandling. Strålningsskador på slutmuskeln är detekterbar med anorektal manometri och ultraljud. Analinkontinensen påverkar livskvaliteten hos drabbade patienter.

### **Studie IV:** Long-term effect of preoperative radiation therapy on anorectal function in patients treated with TME and non-TME-surgery.

*Material & Metod:* 68 patienter som opererats med TME teknik 1995-1996 svarade på samma frågeformulär som i studie III ovan och undersöktes på samma sätt. Resultaten hos TME patienter jämfördes med de 64 patienter som opererats med traditionell teknik i studie III ovan.

*Resultat:* Över hälften (54%) av patienter opererade med TME-kirurgi hade anal inkontinens. Strålbehandling i kombination med TME-kirurgi ökar risken för anal inkontinens ytterligare (64% vs. 35%,  $p=0,024$ ). Patienter med anal inkontinens hade lägre livskvalitet än kontinenta patienter.

*Slutsatser:* TME-kirurgi, särskilt i kombination med strålbehandling, ger ofta anal inkontinens. Anal inkontinens sänker livskvaliteten hos drabbade patienter.

## **Slutsatser**

Studie I-IV ovan visar att:

1. ERUS är en användbar metod för att stadieindela ändtarmstumörer före operation
2. ERUS kan användas för beslut om preoperativ strålbehandling

3. preoperativ strålbehandling ökar risken för hjärt-kärlsjukdom och urininkontinens på lång sikt. Livskvaliteten påverkas inte
4. patienter opererade för rektal cancer med har ofta anal inkontinens med påverkad livskvalitet som följd
5. strålbehandling följt av operation med TME-kirurgi ger ofta anal inkontinens och sänkt livskvalitet.

Behandlingen av ändtarmscancer behöver skräddarsys för varje patient. För att kunna selektera patienter till preoperativ strålbehandling och planera kirurgin behövs en tillförlitlig preoperativ stadiindelning.

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## 11 APPENDIX A: FOLLOW-UP QUESTIONNAIRE

### Follow-up after treatment for rectal cancer

Date of birth:.....

Name:.....

Phone:.....

#### Did you have any surgery done since the primary operation of your rectal cancer?

Yes/No

If yes, please specify.....

#### Have you been admitted to hospital since you had surgery for your rectal cancer?

Yes/No

If yes, where and why?.....

#### Do you have pain?

Yes/No

#### If yes, how often and where?

Once a week or less	More than once a week	Daily
Abdomen	Skeleton	Hips
Muscles	Rectum/Anus	Urinary tract
Elsewhere		

#### Do you use any medications?

Yes/No

#### If yes, which do you use?

.....

#### Do you have any cardiac diseases?

Yes/No

#### Do you have any disturbances in your sexual function?

Yes/No

#### Do you experience urinary incontinence?

Once a week or less	More than once a week	Daily
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#### Do you experience difficulties in emptying your urinary bladder?

Once a week or less	More than once a week	Daily
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#### Do you experience voiding urgency?

Once a week or less	More than once a week	Daily
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**How many times do you empty your bowel per week?**

**How many times do you use laxatives per week?**

**Is your feces generally:**

Hard	Soft	Loose?
Small volume	Normal volume	Large volume?

**Do you have blood in your stools?**

No	Once a week or less	More than once a week	Daily
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**Do you have mucus in your stool?**

No	Once a week or less	More than once a week	Daily
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**Do you experience pain at defecation?**

No	Once a week or less	More than once a week	Daily
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**Do you experience urgency at defecation?**

No	Once a week or less	More than once a week	Daily
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**Do you experience difficulties in emptying your bowels?**

No	Once a week or less	More than once a week	Daily
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**Do you have to manually or digitally extract your feces?**

No	Once a week or less	More than once a week	Daily
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**Can you discriminate between gas and feces in your rectum?**

No	Once a week or less	More than once a week	Daily
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**Do you experience involuntary leakage of gas?**

No	Once a week or less	More than once a week	Daily
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**Do you experience involuntary leakage of loose stools?**

No	Once a week or less	More than once a week	Daily
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**Do you experience involuntary leakage of formed stools?**

No	Once a week or less	More than once a week	Daily
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**Do you experience soiling from your anus?**

No	Once a week or less	More than once a week	Daily
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