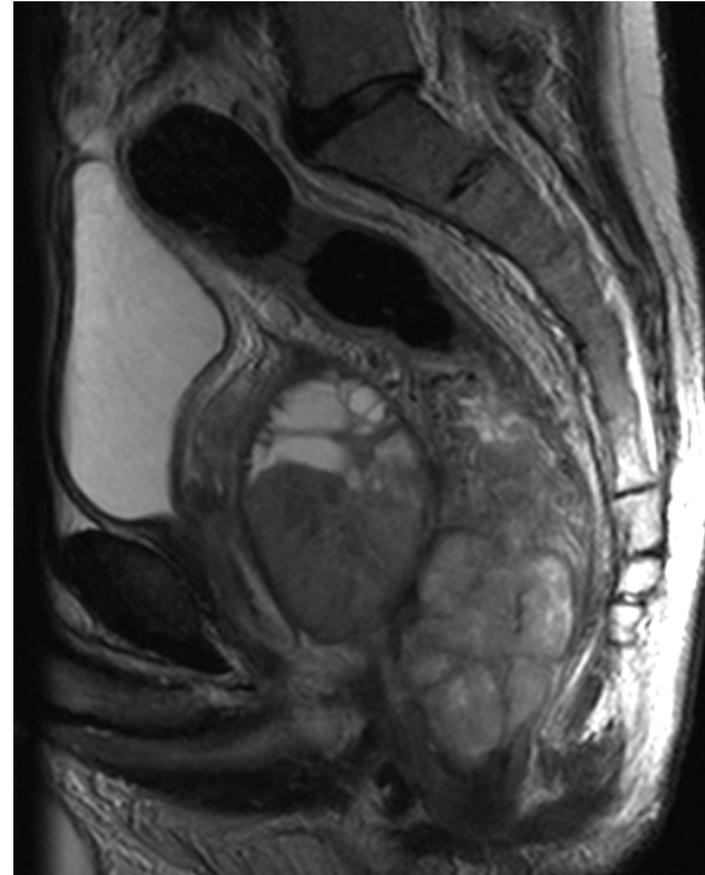


Thesis for doctoral degree (Ph.D.)
2009

Locally Advanced Rectal Cancer

Aspects of Management, Outcome and Quality of Life



Gabriella Jansson Palmer

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Locally Advanced Rectal Cancer: Aspects of Management, Outcome and Quality of Life

Gabriella Jansson Palmer



**Karolinska
Institutet**



**Karolinska
Institutet**

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

Locally Advanced Rectal Cancer

Aspects of Management, Outcome and Quality of Life

Gabriella Jansson Palmer



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Institutet**

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“In my beginning is my end

- - -

In my end is my beginning”

T.S Eliot,

Four quartets, East Coker

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ABSTRACT

Rectal cancer is common in Sweden, with about 1650 patients diagnosed annually. In 10–15% of the patients the tumour is locally advanced at diagnosis, i.e. the cancer is growing outside the mesorectal fascia, into adjacent organs in the pelvis. The incidence of local recurrences, after surgery for primary rectal cancer has decreased as a result of preoperative radiotherapy (RT) and improved surgical techniques, but still the local failure rate is 5–15%.

Treatment of patients with locally advanced primary rectal cancer and recurrent rectal cancer remains a challenge but, with radical surgical resection 5-year survival rates up to 50–60% is reached at dedicated centres.

The aim of this thesis was to analyse management, outcome and the quality of life in patients with both locally advanced primary rectal cancer and locally recurrent rectal cancer, focusing on the preoperative assessment and on multimodality treatment with a multidisciplinary approach.

Two of the studies were population-based and included all patients in the Stockholm-Gotland region with respectively locally advanced primary rectal cancer and local recurrences during 1995–2005. The patients were identified by means of the colorectal cancer registry at the Regional Oncological Centre and their medical records were scrutinised. The other two studies involved patients with locally advanced rectal cancer at a single centre, the Karolinska University Hospital, and treated during 1991–2003.

During 1995–2004 in the Stockholm region, 10% of all rectal cancer patients were found to have a locally advanced primary rectal cancer. In all patients with a potentially curative resection of primary rectal cancer treated during 1995–2003, a local recurrence of rectal cancer was detected in 6% by 2005.

It was concluded that appropriate preoperative radiological tumour staging in patients with locally advanced rectal cancer increased both the proportion of patients who received neo-adjuvant treatment and the rate of potentially curative resections. Local control and survival were improved. Multidisciplinary team (MDT) discussions further enhanced the proportion of curative resections and local control, but no influence on survival was seen.

The overall outcome for patients with locally recurrent rectal cancer was dismal, with a 5-year survival of 9%, but, in patients with a potentially curative resection, an improved estimated 5-year survival of 57% was obtained. A radical resection was necessary for cure and the proportion of curative resections had increased after improved preoperative management and refined surgery compared to an earlier study of local recurrences in Stockholm.

After the introduction of a multimodality treatment programme for patients with rectal cancer, one third of the patients with locally advanced rectal cancer could be cured if a radical resection was performed. Patients with locally advanced primary rectal cancer had a higher rate of curative resections than patients with locally recurrent rectal cancer. The extensive surgery and RT led to a high morbidity.

In measurements of the quality of life in disease-free patients treated for locally advanced rectal cancer several functions, such as role, social and physical function, were low compared with patients treated for primary resectable rectal cancer. This knowledge is valuable for counselling patients preoperatively and for giving adequate postoperative support.

In conclusion, the management of patients with locally advanced rectal cancer can be further improved with adequate preoperative evaluation and staging and increased preoperative neoadjuvant radiochemotherapy followed by extensive surgery. The survival gain of additional adjuvant therapy remains to be studied. Multidisciplinary management of these patients is necessary.

Key word: locally recurrent rectal cancer, locally advanced primary rectal cancer, survival, radiological staging, MDT

LIST OF ABBREVIATIONS

AJCC	American Joint Committee on Cancer
APR	Abdominoperineal resection
CI	Confidence interval
CRM	Circumferential resection margin
CT	Computed tomography
EORTC	European Organization for Research and Treatment of Cancer
Gy	Gray
HRQL	Health-related quality of life
ICD	International Classification of Diseases
IORT	Intraoperative radiotherapy
LAR	Low anterior resection
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
PET	Positron emission tomography
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-CR38	Quality of Life Questionnaire-Colorectal 38
RCT	Radiochemotherapy
ROC	Regional Oncologic Centre
RT	Radiotherapy
SCCSG	Stockholm Colorectal Cancer Study Group
TME	Total mesorectal excision
TNM	Tumour, Nodes, Metastasis (Classification system of staging)
UICC	Union Internationale Contre le Cancer

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by the Roman numerals given below (I–IV).

- I. Palmer G, Martling A, Cedermark B, Holm T.
Preoperative tumour staging with multidisciplinary team assessment improves outcome in locally advanced primary rectal cancer.
In manuscript
- II. Palmer G, Martling A, Cedermark B, Holm T.
A population-based study on the management and outcome in patients with locally recurrent rectal cancer.
Ann Surg Oncol 2007;14(2): 447-54
- III. Palmer G, Martling A, Blomqvist L, Cedermark B, Holm T.
Outcome after the introduction of a multimodality treatment program for locally advanced rectal cancer.
Eur J Sur Oncol 2005;31(7): 727-34
- IV. Palmer G, Martling A, Lagergren P, Cedermark B, Holm T
Quality of life after potentially curative treatment for locally advanced rectal cancer.
Ann Surg Oncol: 2008;15(11):3109-3117

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FOREWORD

Patients with locally advanced rectal cancer have traditionally and until the end of the last century had a most dismal prognosis. The only treatment the patients often received was a diverting stoma and local radiotherapy (RT) because the rectal tumour was considered unresectable. As the local growth of the tumour progressed, patients encountered immense perineal problems involving pain, mucous secretion, odour and fistulas and sinuses. This affected their entire life situation and they often spent the last period of their life isolated from social activities because of the local problems.

With the development of surgical techniques allowing extended resections and with improved radiology and RT, more and more of the locally advanced tumours and recurrences have become resectable. Although the majority of the patients experience postoperative complications, they may recover if the tumour is resected radically and no metastases occur. The majority of the patients will live with one or two stomas during their remaining life.

The Section for Colorectal Surgery at the Karolinska University Hospital, Solna in Stockholm has developed, in cooperation with the Oncological Department at Radiumhemmet and the Radiology Department, a multidisciplinary treatment programme for improved care and treatment of these patients. Patients with locally advanced rectal cancer have influenced the care, and a genuine interest in these patients has grown in all categories of caregivers. This has stimulated the initiation of this thesis.

The aim of the present thesis was to study aspects of locally advanced primary and recurrent rectal cancer in the Stockholm region and of the local treatment programme at the Karolinska University Hospital. The quality of life of the surviving patients after extensive surgery was evaluated in a follow-up study.

INTRODUCTION

Colorectal cancer is the third most common cancer in Sweden. In 2003, according to the Swedish National Cancer Registry, 1644 patient were diagnosed with rectal cancer, which constitutes 30% of all colorectal cancers. There has been a steady increase in the incidence during the last few decades (fig. 1 and 2). However, the mortality is decreasing because of RT and improved surgery.¹⁻⁵ A gender difference with more men being affected has been observed. The incidence in Sweden is 27.5 per 100 000 in males and 15.2 per 100 000 in females. Rectal cancer is most common in the elderly population. The median age at diagnosis is 70 years.

The region of Stockholm and Gotland currently has approximately 1.9 million inhabitants. In 2005 a total of 331 patients were diagnosed with rectal cancer.

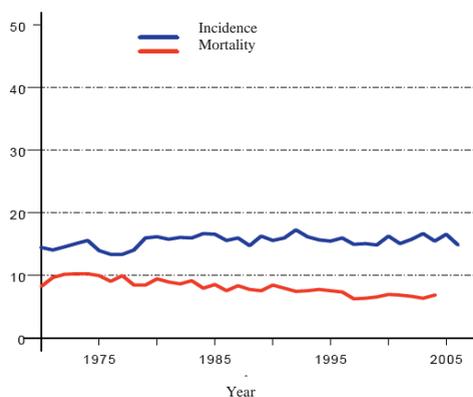


Fig. 1
Age standardised incidence and mortality per 100.000 inhabitants in Sweden 1970-2006 (mortality only to 2004) in women. Data from the Swedish National Cancer Registry.

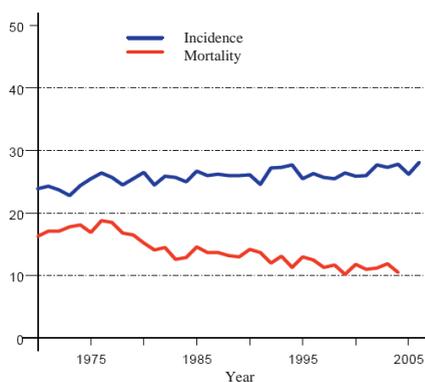


Fig. 2
Age standardised incidence and mortality per 100.000 inhabitants in Sweden 1970-2006 (mortality only to 2004) in men. Data from the Swedish National Cancer Registry.

Locally advanced primary rectal cancer

According to the literature, about 10–15% of patients with rectal cancer have a locally advanced tumour at the time of diagnosis. The actual incidence of locally advanced primary rectal cancer in Sweden is uncertain. The reason why some patients develop large tumours is not known. The biology of the tumour may be more aggressive with fast tumour growth. Patient and doctor delay could also be of importance.

Local recurrences

The incidence of local recurrence after rectal cancer surgery is decreasing as a result of improved surgical techniques and preoperative radiotherapy. Studies from 1970–80 showed a failure rate of as high as 25–40%.^{6,7} After improved surgical techniques and preoperative radiotherapy, the rate has been reduced to 5–15%.^{3,4,8,9} In the Swedish Rectal Cancer Trial, which studied the effect of preoperative RT, the local recurrence rate decreased to 11%.¹⁰ The cumulative risk of local recurrences in irradiated or non-irradiated patients from 1995–2001 according to the Swedish National Colorectal Registry is shown in fig. 3. RT leads to a significant reduction of local recurrences. In dedicated single centre, after the introduction of TME surgery but without RT, local recurrences rates below 4% has been shown.²

In about 30–50% of the patients with recurrent disease, a local recurrence in the pelvis is the only tumour manifestation and it may cause the patient much pain and local problems before death.^{11,12} Local recurrences are predominant after low rectal cancer, but a remaining mesorectum after partial anterior resection in a high rectal cancer can also lead to local recurrence.¹³

Patients with locally recurrent rectal cancer should be referred to dedicated centres where multidisciplinary treatment is possible. An R0 resection is necessary for long-term survival. Dedicated centres show results with around 50% R0 resections reaching a 5-year survival of up to 48%.^{14–16}

The management of patients with recurrent rectal cancer has many similarities to the care of patients with locally advanced primary rectal cancer. In this thesis the two tumour manifestations will be discussed together.

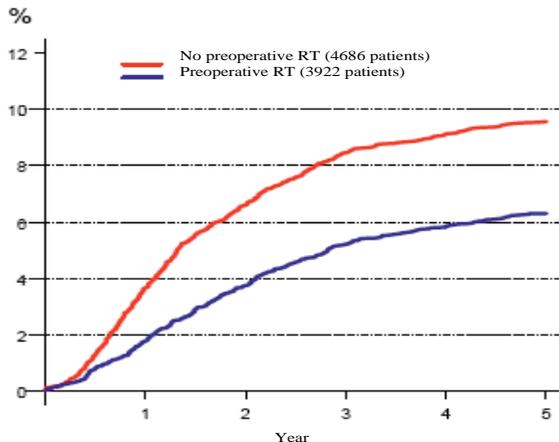


Fig. 3

Cumulative risk for developing local recurrence in patients operated for rectal cancer in 1995–2001, with and without preoperative RT. Data from the Swedish National Quality registry 5-year follow-up of rectal cancer.

The Stockholm Colorectal Cancer Study Group (SCCSG)

The SCCSG was established in 1980 with the purpose of improving the outcome in patients with colorectal cancer. The group represents all nine hospitals in the region and consists of surgeons, oncologists, radiologist and pathologists. Treatment guidelines were established in 1980 and since 1995 all patients with colorectal cancer in Stockholm have been included and prospectively registered in a regional treatment programme. Clinical data are reported to the Regional Oncologic Centre (ROC) by surgeons, oncologists and pathologists. The reports include clinical characteristics such as gender, age, tumour site and stage, type of adjuvant therapy, type of surgery performed, radicality of surgery, postoperative complications and mortality. The pathological reports comprise tumour stage, differentiation, lymph node involvement and total number examined and size and volume of the tumour. Follow-up data containing local recurrences, distant metastases and long-term complications are recorded by the surgeon. The register is regularly validated by cross-checks of medical records and by frequent use in research projects.

The register has been available through the SCCSG for several studies. In the present thesis the clinical data were collected from the ROC registry in combination with a local registry at the Department of Surgery of the Karolinska University Hospital.

BACKGROUND

Definition

The definition of *locally advanced primary rectal cancer* differs in different studies. Historically, a fixed tumour at digital examination was determined to be locally advanced. With the introduction of preoperative work-ups including computer tomography (CT) scans and with the refinement of modern magnetic resonance imaging (MRI) techniques, a “locally advanced tumour” often describes a tumour with adherence to other organs in the pelvis or to pelvic structures. Other studies include bulky T3 tumours with threatened circumferential margins or T4b tumours, tumours with growth onto the peritoneal surface. A radiological T4 tumour is considered when detected growing outside the mesorectal fascia, which can easily be seen on a good quality MRI. However, many pathologists still judge some of these tumours to be T3 as they find it difficult to determine the mesorectal fascia. For T-stage classification see table 1, page 30.

In the present thesis we regard a local primary advanced rectal tumour as either:

- having radiological growth outside the mesorectal fascia
- being judged to be fixed at explorative laparotomy
- growing outside the mesorectal fascia onto adjacent pelvic tissue and/or other organs at surgery or
- having a T4a specimen histopathology, i.e. showing invasion of other organs
- and the distant border of the tumour should be below or at 15 cm from the anal verge.

A *local recurrence* is considered to be situated in the pelvis area close to the area of primary surgery. Ovarian tumour involvements as well as lymph node metastases in the pelvic or inguinal area are regarded as metastatic growth unless continuous overgrowth is noted. Fig. 4 shows the anatomy of the pelvis and rectum.

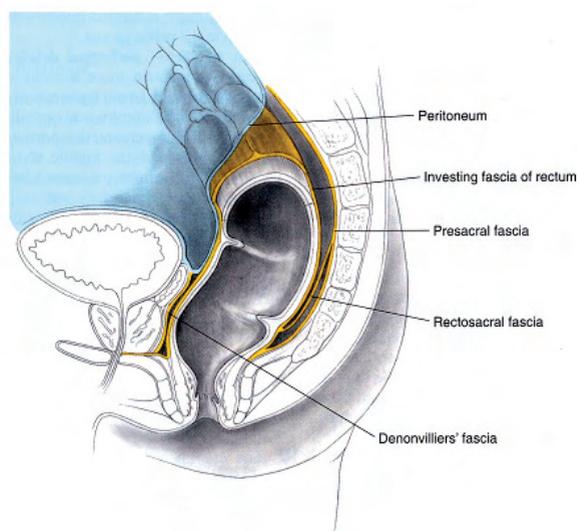


Fig. 4
The anatomy of the pelvis and rectum

Symptoms

Usually, the first symptom of a rectal cancer is a change in bowel habits with constipation or diarrhoea, or a combination of both. The onset is often insidious with a slow increase in bowel frequency. Tenesmus with an urge to defecate is common and it is often the onset of blood and mucus in the stools that brings the patient to the doctor. Anaemia is often a sign of occult bleeding from a right-sided colon cancer, but a patient with advanced rectal cancer is also often anaemic. If the tumour becomes constricting, the patient might develop abdominal colic pain and eventually bowel obstruction.

Localised pain is a sign of a more advanced tumour or a low rectal cancer. The pain depends on spread to local structures, particularly if the tumour invades the sacral nerve plexus. Low tumours become painful when they involve the anal canal.

Patients with locally advanced rectal cancer can also present with recto-vesical, urethral or recto-vaginal fistulas. If the tumour has already grown into a large pelvic mass, the patient may develop leg oedema.

Most rectal cancers have an elective presentation, but they can also present as an emergency with acute obstruction, tumour perforation or massive bleeding.

The clinical manifestation of a local recurrence depends on its site and involvement of adjacent organs. An anastomotic recurrence or recurrence within the rectum will have symptoms similar to those of a primary rectal cancer, such as changes in bowel frequency and rectal bleeding. In spite of routine follow-up after the primary cancer, about two-thirds of the local recurrences present with symptoms.¹⁴ As a rule, the major sign of recurrence is pain, often before any radiological sign of local recurrences can be seen. Overgrowth of the pelvic nerves may give rise to bladder dysfunction and pain.

Diagnosis and clinical staging

Digital examination and procto-rectoscopy

Approximately 75% of rectal cancers in the lower two-thirds of the rectum can be diagnosed by digital examination.¹⁷ An assessment of the size, level, extent of the tumour and its mobility should be made. Digital examination can determine relatively crudely the fixation to adjacent tissues and organs. To determine whether or not a tumour is locally advanced relying only on digital examination is difficult. In a study by Nicholls, the overall accuracy of fixation was 63%.¹⁸ A rigid rectoscopy or a flexible sigmoidoscopy will establish the diagnosis by biopsies and macroscopic appearance.

Imaging modalities

Disseminated disease in the thorax is assessed by pulmonary x-ray or computed tomography (CT) and in the abdomen preferably by CT. Magnetic resonance imaging (MRI) or ultrasound of the liver can also be used. A contrast-enhanced ultrasound of the liver is valuable if the CT has indicated undetermined lesions in the liver.

For local staging of the tumour, endorectal ultrasound, CT and MRI are employed.¹⁹ MRI is superior in determining the local invasion and extramural infiltration of advanced rectal cancer.²⁰⁻²⁴

Endorectal ultrasound is preferred to distinguish T1-T3 tumours. The different layers in the bowel wall are not visible on CT, but pelvic spread and enlarged lymph nodes can be determined.²⁵

Endorectal ultrasound (ERUS)

For many years, ERUS has been the main tool for investigations of local growth in rectal cancer. ERUS has been shown to be a better diagnostic tool for mobile T1-T3 tumours than for more advanced bulky tumours but it is of limited value for visualising extramural growth.^{26, 27} ERUS is also of limited use if the tumour obstructs the rectal lumen or after neoadjuvant therapy.

Magnetic resonance imaging (fig. 5)

The development of MRI has improved the accuracy in rectal cancer staging during the last few decades.²⁰⁻²⁴ Initially, body coils were used which had a lower spatial accuracy than the currently used pelvic phased-array coils. With endoluminal coils, the different layers in the rectal wall can be determined, but the resolution diminishes outside the mesorectum, which leads to the same limitation as with endorectal ultrasonography for extramural growths.

Endoluminal coils are also of limited use for high or constricted tumours.

With pelvic phased-array coils, the mesorectal fascia can be visualised and tumour involvement of the fascia can be determined. It is also possible to visualise overgrowth into adjacent organs, vascular invasion and perineural growth. With MRI, mapping of the tumour growth is possible, which facilitates careful planning of the surgery.²⁸

The determination of lymph node involvement still remains a challenge to the radiologist. Lymph node enlargement and also heterogeneity of the lymph nodes can be seen as an indirect sign of tumour involvement. An iron marker, USPIO may improve the diagnostic accuracy, but the technique is still experimental.²⁹



Fig. 5

MRI locally advanced rectal cancer

Another difficulty is to distinguish the tumour from fibrosis and inflammatory reactions after preoperative RT. Usually, in clinical practice involving patients with locally advanced rectal cancers, an initial MRI is done to determine the tumour growth and select patients for neoadjuvant treatment using radiochemotherapy (RCT). After treatment, a second MRI is done to evaluate the response to the therapy. As the exact delimitation between fibrosis and tumour growth is difficult to determine, the surgeon should use the primary MRI to determine the resection planes. A recent study has shown that the second MRI did not add any information that changed the initial decision regarding surgical planes.³⁰ Furthermore, when the mesorectum is thin, i.e. a limited amount of fat is present, as in low and high situated tumours and in thin patients, the evaluation is more difficult.

Other limitations of MRI are the experience of the radiologist in evaluating the images, the use of suboptimal protocols for the imaging and the cost of the examination.³¹ Contraindications to the examination are metallic implants and claustrophobia.

MRI may also be used for surgical quality control purposes. Comparing the surgical specimen and histopathology with the initial MRI gives a good measurement of the accuracy of the different modalities.^{32 33}

Positron Emission Tomography (fig. 6)

The role of Positron Emission Tomography-Computed Tomography (PET-CT) is under development. Positron-emitting radioisotopes are used to label biochemical compounds as ¹⁸F-labelled 2-fluoro-2-deoxyglucose (FDG) and are injected into the body and the spatial distribution in the body is measured. The aim is to measure biological differences between tumour and normal tissue. Metastases of rectal cancer have been shown to have an increased uptake of 2-deoxyglucose.³⁴ PET-CT can be used to detect local recurrences, distant lymph node involvement and peritoneal spread. Still, PET-CT is mostly used in clinical studies, but it is becoming a valuable tool for early detection of local recurrences and distant metastases, which has led to stage migration in many cases.

FDG-PET has also been shown to be able to predict the effect of the preoperative RCT by comparing the standardised uptake value (SUV) before and after treatment.³⁵

Radiology in local recurrences

The most accurate radiological examination for the diagnosis is MRI, but an early local recurrence may be difficult to distinguish from postoperative fibrosis. Repeated evaluations with MRI may be necessary to establish the recurrence. PET-CT can give additional valuable information. If possible, a biopsy will confirm the diagnosis. In some patients a rise in carcinoembryonic antigen (CEA) in serum is noted, but CEA has a low sensitivity (0.64) to any recurrence.³⁶ Before extensive surgery, it is of the utmost importance to rule out disseminated disease with lymph node involvement above the pelvic region or distant metastases. PET-CT has a high sensitivity for this.



Fig. 6
PET-CT showing disseminated cancer

Preoperative staging

Preoperative staging is based on the clinical and radiological evaluation of the tumour growth and distant spread. The radiologists have adopted the TNM classification (see below) based initially on the histopathology of the specimen, where the evaluation is based on the size and extent of the tumour (T), the absence or presence of regional lymph node metastasis (N) and the absence or presence of distant metastasis (M). An accurate staging is important for selecting the treatment level, for determining the preoperative neoadjuvant treatment and for planning the surgery and the dissection planes. The possibility of achieving a negative circumferential resection margin (CRM) in accordance with the lateral extension and inferior border of the mesorectum is important in the preoperative evaluation of rectal cancer.^{37, 38} The MERCURY Study examined how well a dedicated, standardised MRI examination could predict the CRM and extramural invasion and clarified the importance of MRI in preoperative staging.³⁹ The recently developed concept of “good, bad and ugly” rectal cancers has been used in Stockholm/Uppsala, Sweden and the UK in stratifying the patients into three groups for preoperative treatment (fig. 7)^{40, 41}. The “good” group has no poor prognostic factors on MRI, for neither local nor distant metastases, and needs no preoperative treatment before surgery. The “bad” group has an increased risk for local recurrences and is recommended to have preoperative short-course RT before immediate surgery. The “ugly” group involves patients with an increased risk for both distant and local recurrences and should be given preoperative RCT.⁴⁰ The British stratification differs slightly and has evolved from the MERCURY study addressing the risk of systemic disease, although this risk also increases with the presence of many of the other wellknown risk factors.

National guidelines for the preoperative clinical assessment of rectal cancer have been established during the last 20 years, e.g. the NIH guidelines,⁴² The German Cancer Conference guidelines, UKCCCR recommendations by Bartram and Reznick in 1996 and the SCCSG treatment programmes.⁴³ Compliance with the guidelines may affect the outcome of rectal cancer surgery in terms of survival and local control.⁴⁴

Factors of importance to be determined are:

- Distance from the anus to the lower tumour margin and adequate type of surgery
- Radiological TNM stage
- Histopathology, to ascertain that the tumour is an adenocarcinoma
- Tumour distance to the mesorectal fascia
- Assessment of distant metastases
- Exclusion of synchronous colon tumours

The evaluation of preoperative staging should be discussed at a multidisciplinary team (MDT) conference.^{32, 45, 46}

Fig. 7

Localised rectal cancer assessed by MRI as practised presently in Uppsala and Stockholm, Sweden¹⁾ Published with the permission of Bengt Glimelius.

Favourable 'good' group	Intermediate 'bad' group	Advanced 'ugly' group
Mid/upper rectum T1 – 3b	Mid/upper rectum T3c/d	T4 with overgrowth to prostate, seminal vesicles, base of urinary bladder, pelvic side walls or floor, sacrum positive lateral lymph nodes
Low rectum T1 – 2, T3a N0	Low rectum also includes T3b T4 with peritoneal or vaginal involvement only N1/N2	
CRM clear 5-yr LFR ²⁾ <10%	CRM clear 5-yr LFR ²⁾ 10 – 20%	CRM positive 5-yr LFR ²⁾ 20 – 100%
↓	↓	↓
Primary surgery (TME) ³⁾	Preop 5 x 5 Gy with immediate surgery	Preop RTCT or 5 x 5 Gy with delayed surgery ⁴⁾

¹⁾The algorithm does not primarily address the risk of systemic disease, although this risk also increases with the presence of many of 'the risk factors', however, not necessarily parallel to the local failure rate (LFR).

²⁾Calculated in the group of patients planned for surgery, i.e. irrespective of the surgical outcome. The figures are valid if the surgeon is an experienced rectal cancer surgeon and no pre-treatment is given.

³⁾A local procedure is possible in a few (chiefly pT1, sm1 + 2, N0).

⁴⁾RTCT means radiochemotherapy to 50.4 Gy in 1.8 Gy fractions with 5-fluorouracil. 5 x 5 Gy with delayed surgery is used in patients not fit for RTCT. The relative antitumour efficacy of conventionally fractionated RT or the short-course schedule is not known with any greater certainty^{2,3}

1. Blomqvist L, Glimelius B. The 'good', the 'bad', and the 'ugly' rectal cancers. *Acta Oncol* 2008; 47: 5-8.
2. Courdi A. Fractionation sensitivity and equivalent doses. Commenting the Editorial by Glimelius. *Acta Oncol* 2007; 46: 395-6; author reply 96.
3. Suwinski R, Wzietek I, Tarnawski R, Namysl-Kaletka A, Kryj M, Chmielarz A, Wydmanski J. Moderately low alpha/beta ratio for rectal cancer may best explain the outcome of three fractionation schedules of preoperative radiotherapy. *Int J Radiat Oncol Biol Phys* 2007; 69: 793-9.

Multidisciplinary team conferences

In an MDT conference, radiologists, pathologists, surgeons, oncologists and associated clinical nurses are engaged in deciding on the treatment for each individual patient (fig. 8). All treatments should be individualised and, based on the available knowledge and inclusion in studies, decisions on neoadjuvant RT and/or chemotherapy should be taken. Postoperatively, the histopathology report for each patient should be discussed and the patient should be considered for adjuvant treatment. If a hospital is not able to arrange an MDT conference, arrangements to join a larger centre's MDT conference can be made, for example, using telecommunication. A British study has shown that rectal cancer patients discussed at MDT meetings had lower rates of CRM involvement (1% versus 26%) and patients with irresectable tumours could be selected for alternative treatments.⁴⁵ A recent study on metastatic surgery in colorectal cancer indicated that patients with rectal cancer and distant metastases discussed at MDT meetings were referred more often to surgery.⁴⁶



Fig. 8
MDT Conference

Preoperative treatment

Radiotherapy

Until the beginning of the 1990s surgery was the standard treatment for rectal cancer. Many studies during the 1980–90s have shown that preoperative RT reduces local recurrences and increases the cancer-specific survival.^{47, 48} The aim of RT is to eliminate microscopical peripheral tumour cells in the peritumoural tissue, thus gaining a better local control. In Europe, preoperative RT is now standard for T3–T4 tumours, while in the United States, postoperative RT is still frequent. The advantage of preoperative treatment has been demonstrated in several European studies with a marked reduction in local recurrences.^{4, 49, 50}

The advantage of postoperative RT is its selective value as patients with a high risk of recurrence can be identified after histopathological examination of the specimen. The risk of over-treating the patients with RT is reduced. A disadvantage is the risk of small bowel toxicity as the small bowel tends to fall down in the pelvis after rectal resection. Postoperative RT also has a lower compliance because postoperative complications prevent RT. The German Rectal Cancer Study group performed a randomised study comparing preoperative RCT with postoperative RCT for locally advanced rectal cancer and showed improved local control and less toxicity with preoperative RCT, though no survival benefit.⁵¹

The optimal fraction of radiation has been tested in several studies.^{49, 52, 53} In Sweden, there is an ongoing 3-armed prospective randomised study on T1-T3 tumours (Stockholm III) treated with a short course of 5 Gy x 5 followed by surgery either immediately or after 6 weeks or a long course with a lower fractionation dose of 2 Gy x 25 followed by surgery after 6-8 weeks. This study also aims to determine the optimal timing of surgery after RT. In a single-centre study, postponing the surgery after RCT for more than 8 weeks was shown to result in fewer postoperative complications such as anastomotic leakage, but no adverse oncological consequences.⁵⁴

A complete response, in which no viable residual tumour can be identified, is noted in up to 20% of cases after preoperative treatment, especially when combined with neoadjuvant chemotherapy.⁵⁵⁻⁵⁷

Patients with locally advanced rectal cancer in Sweden and in most European countries are usually treated with preoperative RT using a long-course low fraction of 40–50 Gy. The aim is to achieve a downstaging and downsizing effect with tumour regression,⁵⁸⁻⁶⁰ thereby allowing resection with free distant and lateral margins. Delaying surgery for 6–8 weeks after RT was shown to have a more pronounced effect on downstaging in the Lyon R90-01 trial.⁶¹ Other recent studies have demonstrated improved local control after RCT with delayed surgery in advanced rectal cancer.⁵⁸⁻⁶⁰ However, a Polish trial showed no beneficial effect of RCT, compared to a short course of 5x5 Gy and immediate surgery, on long-term survival or local control.⁶² In another study including patients not eligible for RCT because of advanced age in combination with severe co-morbidity, the patients had RT with 5x5 Gy and delayed surgery; the regimen was found to result in a high proportion of radical surgery and was well tolerated by the patients.⁶³

The RT is currently administered using a four-field technique; from perineum to promontory (L5–S1), extending laterally to the bony side-walls of the pelvis and from the middle of the caput femori to the anterior aspect of the sacrum (Fig. 9). The fields have been standardised, but at present the linear accelerators in use have multileaf collimators that customise the irradiated volume to individualise the field with the purpose of minimising irradiation of other areas. In high situated tumours, the anal sphincters are shielded. Organs at risk for radiation injury are the small bowel, anal sphincter, bladder, ureters and nerves.

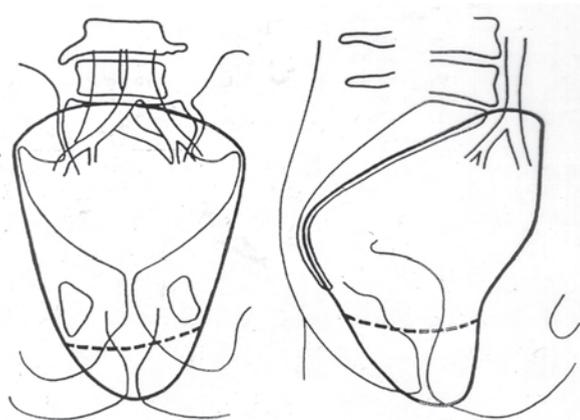


Fig. 9
Target volume; frontal and sagittal image of the pelvis
Organs at risk: small bowel, anal sphincter, nerves, bladder and ureters
Dotted line indicates blocking possibilities of anal sphincter.

Early complications of RT are nausea, diarrhoea, dermatitis, enteritis and proctitis. Postoperative complications after RCT or RT alone, such as anastomotic leakage and disturbed perineal and pelvic healing, have been discussed and studies have shown up to 28% of anastomotic leakage if no defunctioning stoma is established concomitantly with primary anastomoses in rectal cancer surgery.^{54, 64, 65}

Well-known long-term complications are bowel obstruction, anal sphincter damage with incontinence, diarrhoea, sexual dysfunction, urinary dysfunction, osteoradionecrosis and peripheral nerve injuries.⁶⁶⁻⁶⁹ There is a risk of occurrence of secondary cancer in the irradiated field after RT or RCT. In a recent Swedish study the risk was almost doubled in patients treated with RT compared with those not receiving RT.⁷⁰ Overall, about 7% developed a secondary cancer. The most common secondary cancers were cancers of the prostate, colon and urinary bladder. Even a non-significant increase was seen in organs outside the irradiated field. Although secondary cancer were more common in the RT group, the favourable effect of RT appears to dominate with a reduced risk of local recurrences.

Following preoperative treatment, a second MRI is performed to evaluate tumour regression. A problem encountered in analysing the second MRI is distinguishing tumorous tissue from fibrosis induced by the radiation. As it is difficult to discern distinct borders of the tumour, most surgeons schedule surgery after the first MRI. An unpublished study from our institution implied that there were islands of isolated tumour cells in the fibrotic tissue in up to 50% of the specimen, which supports the use of wider resection planes.

Intraoperative radiotherapy (IORT)

The role of IORT is still controversial. IORT implies giving RT as a single dose during the surgery after resection of the tumour at the site of the previous tumour bed. IORT produces a higher localised biological effect compared to fractionated external RT. It also has the advantage of delivering radiation accurately to the desired target while adjacent normal structures can be displaced or shielded from the irradiation field.

Specialised single centres around the world use different forms and schedules for IORT. No randomised study has been done and the results are ambiguous in studies where no overall survival benefit has been demonstrated. Series of cases have shown improved local control especially after R1 resections.⁷¹⁻⁷⁶ One argument put forward is that a true R0 resection does not leave any cancer cells, but as it is not always easy to distinguish fibrosis from remaining cancer tissue and, in clinical practice, some patients with an R0 resection may benefit from IORT.⁷⁷ A Norwegian study showed no major effect of IORT.⁷⁸ In Denmark the Colorectal Centre in Aarhus uses brachytherapy with intermittent booster doses for three days postoperatively and considers the results promising (personal communication).

At the colorectal unit at Karolinska University Hospital, IORT has been possible since 1991. The indications have changed from irradiation of unresectable macroscopically remaining tumours to use in recent years at the discretion of the surgeon when there are minimal free circumferential margins at the resection site, leaving the suspicion of an R1 resection. Most patients receive a dose of 15–20 Gy localised at the site of remaining tumour cells.

With improved surgical techniques and skill, achieving more R0 resections, the need for IORT has probably diminished.

Chemotherapy

The addition of neoadjuvant chemotherapy with fluorouracil and leucovorin (FLv) together with RT in advanced rectal cancer has been shown to improve the downstaging and to reduce the incidence of local recurrence, but no overall survival benefits had been demonstrated until recently.^{58, 60}

A Nordic randomised study on locally advanced rectal cancer (LARC) with or without neoadjuvant chemotherapy indicated improved local control and cancer-specific survival with the addition of FLv, in addition to a higher complete response rate (18% compared to 7%) with RT alone.⁵⁹

A disadvantage was an increased frequency of diarrhoea during the treatment period.

Phase II studies have shown oxaliplatin in combination with fluorouracil to increase the radiosensitivity.⁷⁹⁻⁸¹

In the Swedish CORGI-L phase II study on unresectable rectal and colon cancer and recurrences, treated with capecitabine and oxaliplatin in combination with RT, showed a partial or complete response in 58% of the patients. Seventy-nine per cent could be operated upon and 92% had an R0 resection. However, the toxicity was high and 22% had grade 3–4 diarrhoea (unpublished results).

Today, the standard treatment today for locally advanced rectal cancer in Sweden is 50.4 Gy in 28 fractions with oral capecitabine 825 mg/m² x 2 every day of RT.

If the patient has resectable distant metastases, a combination with radiotherapy/fluorouracil/oxalaplatin (RT-FLOX) is recommended. In patients with irresectable distant metastases, palliative treatment with chemotherapy alone is given, followed by RT if the patient gets local symptoms of the rectal cancer.

Targeted treatment with monoclonal antibodies such as cetuximab, anti-EGFR (epidermal growth factor), and bevacizumab, anti-VEGF (vascular endothelial growth factor), are showing promising results in recent studies.^{82, 83} An ongoing randomised European two-armed study, the Expert-C trial with Xeloda and cetuximab, in combination with RT in one arm or only Xeloda-RT in the other, will probably reveal interesting results of targeted treatment.⁸⁴

Adjuvant postoperative treatment for patients with rectal cancer and regional lymph node metastases has not proved to have any survival benefit in contrast to in colon cancer stage III and should mainly be given to patients included in studies.⁸⁵

Immunotherapy with proliferation of the patient's own anti-tumoural antibodies is used on an experimental basis.

For local recurrences, the same principles should be applied if the patient has not been given RT before the primary resection. Otherwise, the option of immediate surgery or preoperative chemotherapy should be raised at a MDT conference. IORT could be considered if remaining tumorous tissue is suspected.

Surgery

The earliest described surgical resections for rectal cancer were through the perineum in 1739 by Faget and in 1826 by Lisfranc.⁸⁶ Rectal surgery had a high mortality, morbidity and a recurrence rate of 95% until Miles developed the technique of abdominoperineal resection (APR) in 1908 after pathological studies on the spread of rectal cancer.⁸⁷ Miles' operation became the golden standard for the beginning of the century. In the early 1940s the sphincter-saving operations with an

anastomosis via an abdominal approach, mainly for high rectal tumours, became popular through the work of Dixon at the Mayo Clinic.⁸⁸ In the 1970s, after the introduction of stapling instruments, even low anastomoses were shown to be reliable. The dissection of the rectum was often done bluntly with the risk of nerve injury. The rates of impotency and micturial disturbances were high. The local recurrence rates were reported to range up to 40%.^{2, 12, 89}

In 1982 Heald introduced the concept of total mesorectal excision (TME) in which the resection follows the embryological avascular plane outside the mesorectal fascia which encloses the rectum with perirectal fat, blood vessels, lymph nodes and nerves.² The sharp dissection under direct vision allows removal of the rectum with the mesorectum down to the pelvic floor with preservation of the hypogastric and sacral nerves, leaving the sexual and micturial functions intact.⁹⁰ As early as in 1986 Heald reported a local recurrence rate of less than 5% without preoperative RT.⁹¹ The technique was introduced early in the Scandinavian countries. In Stockholm the TME Project, a collaborative teaching project with surgical and pathological workshops, led to an increased specialisation in rectal cancer surgery.⁹² In addition local control and cancer-specific survival was significantly improved.³ TME technique is now well established and an overall local recurrence rate of around 10% is reported from dedicated centres.^{3, 93}

For high and midrectal tumours, a low anterior resection (LAR) is performed, in which the rectum is resected using the TME technique and the continuity is restored with an anastomosis using a circular stapling device. In older patients a Hartmann's procedure may be performed, in which the bowel is resected, but the remaining rectum is left in situ and closed in the pelvis and a permanent stoma is established.

In patients with low tumours an APR is the most common surgical procedure or, alternatively, an ultra-low anterior resection with an inter-sphincteric resection. For T1 rectal cancer, a local excision can be employed, especially in older patients with unstable general health. The risk of local recurrences is not to be underestimated.⁹⁴

Surgery in locally advanced rectal cancer

Depending on tumour growth and the expected reconstruction of organs, the operating team is often multidisciplinary, comprising vascular surgeons, urological surgeons and plastic surgeons besides the colorectal surgeon. It is of the utmost importance to have good preoperative planning and discussion at the multidisciplinary conferences. A co-ordination contact nurse is most valuable in the planning and organisation of the team around the patient.

To achieve long-term survival in patients with locally advanced rectal cancer, it is necessary to perform an R0 resection.^{95, 96} An extended TME resection is necessary, with resection outside the mesorectal fascia, including resection of the involved adjacent organs en bloc. All structures that are adherent to the tumour should be resected because it is not possible to determine if adhesions are malignant or inflammatory. About 50% of the adhesions prove to be malignant and will result in a high degree of recurrences.⁹⁷ IORT may be added as it is often difficult to determine if the CRM consists of fibrotic or remaining cancerous tissue,^{15, 77}

The patient has sometimes received a temporary diverting sigmoid stoma before preoperative RCT to treat obstruction from a large, bulky rectal tumour. In the main operation the first step is to resect all tumour-involved organs en bloc – if necessary the ureters, bladder, small bowel, pelvic floor, nerves, blood vessels and sacrum. In men, the prostate and seminal vesicles and, in women, the uterus, ovaries and vagina are removed if necessary. If all organs in the pelvis are resected, a pelvic

excenteration is performed; more frequently, only one or two other organs are resected (fig. 10). When performing an APR we routinely start with the abdominal part and the rectal resection with adjacent organs en bloc is dissected down to the inferior hypogastric plexus, to the proximal part of the coccyx dorsally and ventrally just below the seminal vesicles in men and to the cervix uteri in women. The patient is then turned to a prone jack-knife position and the perineal part of the operation is performed. The specimen is resected through the perineal excision.⁹⁸

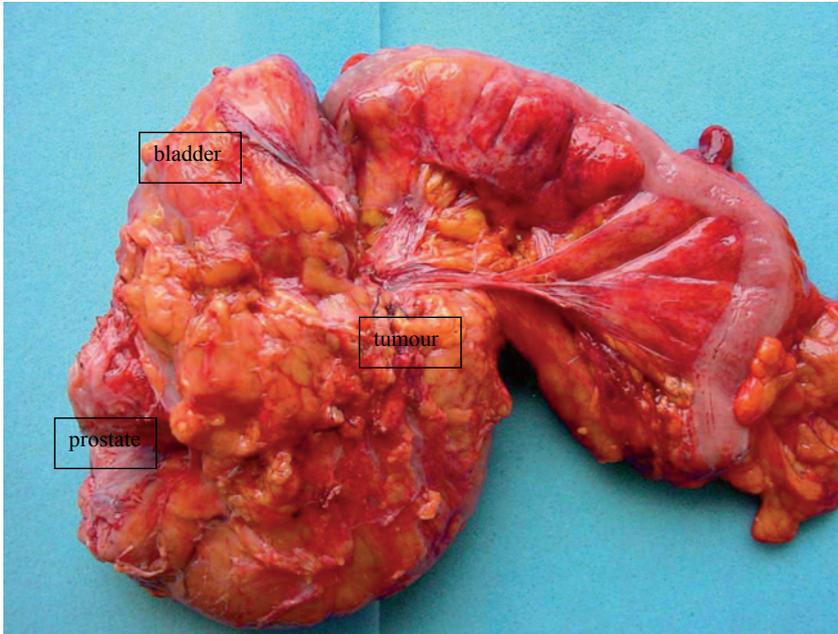


Fig. 10
En bloc resected specimen with rectum, bladder and prostate.

Reconstruction

When the abdominal dissection is completed, the following step is to reconstruct the resected organs. The continuity of the colon and rectum is established, if possible, with an anastomosis (LAR) or, in the case of a low tumour, a permanent colostomy is constructed (APR).

As a substitute for the urinary bladder, a Bricker deviation can be made from a segment of the small intestine to which the ureters are anastomosed to the proximal end and the distant end is taken out as a stoma. The intestine can also be sutured to the remaining urethra, i.e. a Studer substitute, avoiding a urostoma. If only a short segment of the ureter has to be resected with the tumour, an end-to-end anastomosis may be possible. If it is in close proximity of the bladder, the ureter can be tunnelled into the top of the bladder and sutured. The bladder can be mobilised to reduce straining. If this is not possible, construction of a flap of the bladder is useful to anastomose with the ureter, or a segment of the small intestine can also be used as a ureter substitute.

In the female, a neovagina can be reconstructed with a flap from the skin in the perineum or, if only partially resected, directly sutured to a narrower vagina. If the woman is premenopausal, she should be given an oestrogen substitute postoperatively. Blood vessels can be reconstructed with endovascular grafts or by bypass operations.

The final step is closure of the abdomen, and construction of stomas and reconstruction of the perineum. If the perineal defect is large and most of the pelvic floor is resected, a perineal reconstruction can be made by means of a muscle gluteus maximum flap, a muscle gracilis flap or a rectus abdominus flap. The gluteal flaps are preferred at our institution.⁹⁸ The advantages of gluteal flaps are that they are still enervated, which gives good postoperative function with a contractible muscle, they are technical easy to perform and they give good coverage to the perineal defect.

Surgery in local recurrences

Treatment of local recurrences is similar to the treatment of a primary advanced rectal cancer. Most careful mapping of the tumour growth by MRI is necessary. If the patient has not received RCT before surgery of the primary rectal cancer, long-term RT in combination with chemotherapy is recommended.⁵⁹ Otherwise, immediate surgery is performed if the local recurrence is resectable. The same principles as mentioned above are applied to surgery for local recurrences. The surgical approach depends on the location, but often a wide resection of the tumour, including adjacent organs in the pelvis, is performed; it is often necessary to resect the pelvic sidewalls and the sacrum. However, the surgical planes are often distorted from previous surgery and postoperative fibrotic tissue may be difficult to distinguish from tumours. IORT may be used as in surgery of locally advanced primary rectal cancer. APR and pelvic exenterations are performed more often.

Histopathology

The histopathological staging of the specimen is important for predicting the prognosis and to select patients for adjuvant treatment. Several systems for the classification of rectal cancer are in existence. All the different staging systems are based on tumour penetration into the rectal wall, involvement of lymph nodes and the presence of distant metastases. Since 1932 Dukes' morphological classification system has been the prevailing one. It has been modified several times with different categorisations of depth of invasion and lymph node involvement.⁹⁹ In 1967 Turnbull added stage D, indicating concomitant distant metastasis.¹⁰⁰ To provide a more clinico-pathological system, the TNM system was developed by Denoix in the 1950s and adapted by the Union International Contre le Cancer (UICC). In collaboration with the American Joint Committee on Cancer (AJCC), a staging system indicating the prognostic values was developed based on the TNM system and paralleling the Dukes system. See table 1 for comparisons of the different systems.

Table 1. Systems for Classification of Rectal Cancers

AJCC/UICC staging system	TNM system	Dukes' classification
Stage I	T1-2 N0 M0 T1= Involvement of the submucosa T2= Invasion into but not through the muscularis propria N0= No nodal involvement M0= No distant metastases	A Tumour limited to rectal wall
Stage II	T3-4 N0 M0 T3= Penetration through the muscularis propria into the serosa or perirectal fat T3a= Minimal invasion:<1 mm beyond the border of the muscularis propria T3b= Slight invasion:1-5 mm beyond the border of the muscularis propria T3c= Moderate invasion:>5-15 mm beyond the border of the muscularis propria T3d=Extensive invasion:>15 mm beyond the border of the muscularis propria T4a= Invasion of other organs T4b= Involvement of free peritoneal cavity	B Tumour growth outside the rectal wall
Stage III	Any T N1-2 M0 N1= Metastases in 1-3 perirectal lymph nodes N2= Metastases in ≥ 4 perirectal lymph nodes	C Lymph node involvement
Stage IV	Any T Any N M1 M1= Distant metastases	D Distant metastases

The residual status of the local tumour and distant metastases after surgery is described by the residual tumour classification (R) proposed by the UICC in 1987. Hermanek has shown that the residual classification is a strong predictor of local recurrences and survival.¹⁰¹ An R1 resection includes all specimens with remaining tumour at any resection margin or perforated tumours (table 2).

Table 2. Residual Tumour classification

R0	No residual tumour
R1	Microscopical residual tumour
R2	Macroscopical residual tumour

A non-curative operation is an operation in which tumours have been left behind either owing to the presence of distant metastases or because of the presence of residual local disease.

A curative operation is defined as a procedure in which metastases have been excluded by preoperative imaging and an R0 resection is achieved locally.

Prognosis

The tumour stage and residual tumour are of major importance as prognostic factors.¹⁰¹ A careful and meticulous histopathological examination of the specimen by the pathologist is necessary (fig. 11). In TME surgery, positive circumferential resection margin (CRM) has a strongly negative impact on local recurrences and distant metastases.^{38, 102, 103} CRM corresponds to the non-peritonealised surface of the resected specimen created by dissection of the subperitoneal aspect at surgery. In locally incomplete resections, tumour is found in CRM in more than 90%.¹⁰⁴

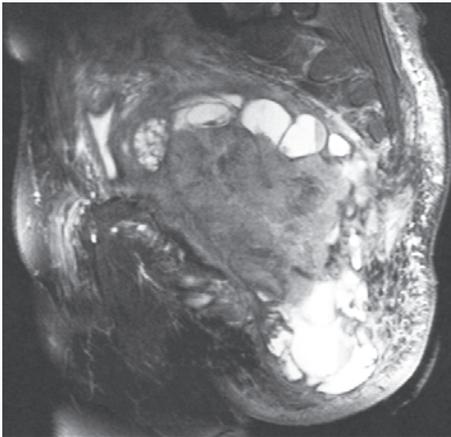
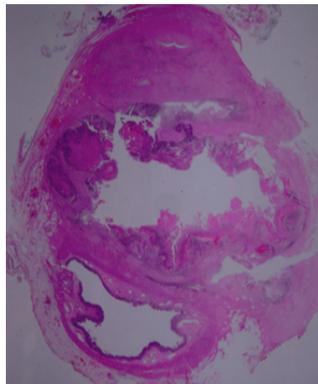
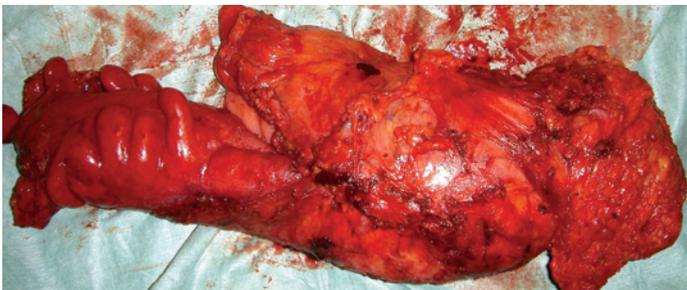


Fig. 11
Preoperative MRI and histopathological assessment of a specimen of locally advanced primary rectal cancer resected en bloc with the bladder, prostate and pelvic floor.



Another factor of importance is tumour height.¹⁰⁵ Patients with low tumour have a more dismal prognosis. Vascular and lymphatic invasion and perineural growth also have a negative prognostic value.^{106, 107}

The macroscopic appearance of the specimen is important, as shown by Nagtegaal et al.¹⁰⁸ Incompleteness of the mesorectal envelope indicates a risk of a positive CRM in TME-resected rectal cancer. However, recurrences occur more often in patients with an incomplete mesorectum even with a negative CRM, so the macroscopic appearance of the specimen is an additional prognostic factor. As discussed in the section on surgery, for a locally advanced rectal cancer, en bloc resection is the golden standard in order to avoid the spread of tumour cells at surgery.^{97, 109, 110}

At dedicated centres, 5-year survival rates of 50–60% are reported for locally advanced rectal cancer.^{76, 109, 111, 112} The survival is often better for primary advanced rectal cancer than for locally recurrent rectal cancer as shown in a study from the University of Texas, Anderson Cancer Centre, where primary rectal cancer had a 5-year survival of 65% after pelvic exenterations compared to a 5-years survival of 22% of local recurrences.¹¹² Other studies show overall survival rates of 18–31% for local recurrences.^{15, 111, 113} If R0 resections are achieved, 5-year survival rates of 37–52% are observed.^{14, 15} After an R0 resection in primary advanced rectal cancer, a 5-year survival of up to 72% is observed.¹⁵ The local recurrence rates range between 9% and 68 %, with lower rates after primary advanced rectal cancer compared to locally advanced rectal cancer.^{111, 112}

If the local recurrence is irresectable, i.e. there is overgrowth to S1 or higher or involves sciatic nerves, palliative radiotherapy is recommended if the patient develops pain or soiling problems. With palliative treatment the median survival time is 14 months, and the 5-year survival is dismal, i.e. less than 5%.¹¹⁴

An untreated local recurrence can cause the patient immense local distress with bleeding, soiling and odour as the recurrence erodes the pelvis and develops into an open sinus in the perineum, leading to a poor remaining quality of life.

Distant metastases remain challenges as overall 40–50% of patients with rectal cancer suffer recurrences as disseminated disease.

Short and long-term morbidity

Patients who have undergone treatment for locally advanced rectal cancer have a high reported postoperative morbidity of up to 40–50%.^{112, 115} Complications may be either of the *infectious or cardiovascular* type, such as pneumonia, vascular thrombosis and urinary infections or *surgical*, such as bleeding, wound infections, wound rupture, defecation disorders, pain, intestinal obstruction and anastomotic leakage with pelvic abscesses. It is of the utmost importance that these patients are carefully observed and mobilised early.

Long-term complications, such as bowel dysfunction, anal incontinence, mictural disturbances and sexual problems, are well documented, as well as fistulas, sacral fractures and small bowel obstructions.^{116, 117} In long-term follow-ups of functional outcomes, pain and fatigue are predominant in 40–50% of the patients.¹¹⁸ The complications may be due to a late radiation effect¹¹⁹ or the surgical trauma.¹²⁰ Pollack et al. have studied long-term effects after preoperative RT as compared to surgery alone and found an increased risk for cardiovascular events, urinary incontinence, diarrhoea and anal incontinence.⁶⁹ However, the study did not include patients with locally advanced rectal cancer. Since the most importance factor for cure in locally advanced rectal cancer is achieving

an R0 resection at surgery, it is often necessary to resect nerve bundles and vessels in the pelvis, which leads to impotence and mictural complications.¹²⁰ Male sexual problems are well studied, but female sexuality after major surgery is scarcely documented.

In recent studies the postoperative mortality for advanced rectal cancer is as low as 0–3.5% probably because of careful selection of the patients preoperatively and improvements in postoperative critical care.^{16, 112, 121}

Health-related quality of life (HRQL) in patients with advanced rectal cancer

Quality of life (QoL) is a concept with a broad range of definitions and no generally accepted definition exists. The World Health Organisation (WHO) defined health in 1946 as “a state of complete physical, mental and social well-being and not only the absence of disease or infirmity”.¹²² QoL is multidimensional, including physical, emotional, social and functional aspects and is experienced from a subjective aspect, since it is the patient’s own point of view that is measured. Quality of life is also affected by disease and changes over time.

The health-related quality of life (HRQL) is a more recent concept based on the WHO definition of health but differs from QoL’s more general sense as it focuses on aspects of life that are affected by clinical and medical interventions. Individual patients may perceive the same disease and treatment differently, indicating that certain aspects of life are of importance to one individual but may have no relevance for another. Cella defines the subjective perception of the quality of life as follows: “Quality of life refers to patients appraisal and satisfaction with the current level of functioning as compared to what they perceive to be possible or ideal”.¹²³ The incorporation of HRQL data will provide additional and complementary outcomes to more conventional outcomes such as survival, disease-free interval and rate of local recurrences.

In this thesis the concept of health-related quality of life is used as an instrument to see how the disease advanced rectal cancer and its treatments affect the patient. Several studies have measured the quality of life after preoperative RT and also after surgery for LAR as compared to APR, but HRQL measurements of patients with locally advanced rectal cancer are rare.¹²⁴⁻¹²⁸

Rectal cancer does not only affect the physical aspect of patients’ lives, it has been shown to have an impact on mental, emotional and social functioning of the patient. The feeling of life being threatened to be burdened with cancer, the sensation of powerlessness and the uncertainty of the future will all affect the quality of life.

It is important to identify the aspects of HRQL that may be affected by the treatment. Patients who have gone through complicated treatments followed by extensive surgery and a long postoperative recovery period may validate their present life from a new point of view. Even if their physical health might be impaired, other factors such as social well-being, relations with family and close friends can become more important than before. This may be due to an adaptation to their changed life situation and the change of perception and evaluation of what is important in life. This phenomenon has been called response shift in the literature of quality- of- life research.¹²⁹ It has been shown that patients with severe diseases report similar or superior levels of quality of life than less severely ill patients.

There is a wide variety of methods to measure the quality of life; it can be done by means of structured or unstructured interviews or questionnaires with either open answers or multiple-choice responses. The most common way is by written questionnaires that the patients fill in by themselves. Several frequently used and well-constructed questionnaires have been developed the last few decades.¹³⁰⁻¹³² A questionnaires should show good reliability and validity and also responsiveness to changes over time.

There exist several types of questionnaires:

Generic instruments are used to obtain a more general health profile, irrespective of illness or condition, that allows comparisons between groups and the general population but are less sensitive, such as the SF-36¹³² or the Nottingham Health Profile.¹³³

Disease-specific instruments are designed to focus on a specific disease such as a chronic illness like asthma or cancer, which allows detection of differences after treatment, such as the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30¹³⁰ or the Functional Assessment of Cancer Therapy-General (FACT-G).¹³⁴ Both the EORTC and the FACT have also developed tumour-specific modules for different cancers such as the colorectal module EORTC QLQ-CR38.¹³¹

Domain-specific instruments focusing on specific aspects of health, for example the questionnaires on rectal functioning such as the Cleveland Clinic Faecal incontinence Score.¹³⁵

One purpose of measuring the quality of life is to add another outcome factor particularly in randomised studies, i.e. a measure of the quality of life with a certain therapy compared to without it, for example, to assess side effects of radiotherapy in rectal cancer.^{68, 119} Quality of life measurements are also valuable for evaluations of the remaining complications of therapies, for examples, or to determine the effect of advanced surgery with permanent stomas in rectal cancer.^{127, 136-138} Moreover, it is an important tool for supporting advice and information to patients and also for socio-economic health evaluations in the public health system. Recent studies have demonstrated the possibility of using quality of life factors as a predictor of mortality.^{139, 140} For new and advanced cancer therapy, it is useful to quantify the quality of the prolonged survival.

Nowadays more and more patients demand full information about the consequences of their disease and treatment and the impact on their quality of life. To cancer treatment outcomes like overall survival, local recurrences and disease-free survival, the quality of life should be added.

AIMS OF THE THESIS

The **overall aim** of these studies was to analyse the management, disease outcome and quality of life in patients with locally advanced primary and recurrent rectal cancer.

The **specific aims** were to

- assess the relation between the quality of preoperative tumour assessment and the outcome in patients with locally advanced primary rectal cancer;
- evaluate the management and outcome in patients with locally recurrent rectal cancer;
- review the overall treatment results after the introduction of a multimodality programme in patients with locally advanced rectal cancer;
- assess the long-term health-related quality of life in patients after extensive surgery for locally advanced rectal cancer.

PATIENTS AND METHODS

The studies included in this thesis were conducted to examine factors influencing the outcome after surgery in patients with advanced rectal cancer. The limited number of patients in a single hospital makes it difficult to obtain an adequate number of patients for clinically significant studies. We have conducted two population-based studies in the Stockholm-Gotland region (papers I and II) and two single-centre studies (papers III and IV). The origin of the cohort and the number of patients in each study are presented in table 3.

Table 3. Patients with rectal cancer included in the studies

Paper	cohort	Data collected	Number of patients in the study	Follow- up
I	Stockholm-Gotland region	1995-2004	2909 patients with rectal cancer 303 primary advanced rectal cancer	1995 to March 2008
II	Stockholm-Gotland region	1995-2003 1995-2004	2318 patients with rectal cancer 141 patients with local recurrences	1995 to Aug 2005
III	Karolinska University Hospital	1991-2002	58 primary advanced rectal cancer 64 local recurrent rectal cancer	1991 to April 2003
IV	Karolinska University Hospital	1991-2003 2005	142 patients underwent surgery for advanced rectal cancer 53 alive 43 in study	March 2005 to Dec 2006

The population in studies I and II were selected from data from the Regional Oncological Registry for the Stockholm-Gotland region.

In study I the patients with primary advanced rectal cancer were selected indirectly, as patients with primary advanced rectal cancer do not have a distinct code in the International Classification of Diseases (ICD); they are included in the classification of rectal cancer (C20). To be able to distinguish them, patients with rectal cancer who had histopathologically been classified as T4 tumours, recorded excision of other organs, long RT or RCT, non-radical resections or not resected at all, were selected. These medical reports were scrutinised and patients were selected who, either in a preoperative evaluation, or during the surgical procedure or at the final histopathology, were considered to have an advanced rectal cancer (table 4). An assessment of their preoperative work-up was made and such outcome factors as residual tumour status, local recurrences, survival and cancer-specific death were recorded. The median follow-up time was 88 (31–159) months.

Table 4. Evaluation of T4-stage

	Total n=303	Group1 n=65	Group2 n=99	Group 3 n=139
Preoperative assessment	186 (61)	62 (95)	69 (70)	55(40)
Surgical assessment	245 (81)	49 (75)	76 (77)	120 (86)
Histopathology	170 (56)	30 (46)	55 (56)	85 (61)

Values in parenthesis are percentage.

Study II included patients registered for a local recurrence (ICD C78.5 correlated with a previous diagnosis of C20). The medical records were analysed and a registered local recurrence was only accepted if the patients had previously had an R0 or R1 resection of the primary rectal cancer. A recurrence after an R2 resection was not recorded since a residual macroscopic tumour was left at the primary operation. Data on the treatment modalities and prognosis were retrieved and compared to a previously studied cohort of patients with local recurrences diagnosed during 1980–91. The median follow-up period was 12 (0–103) months.

In papers III and IV the cohorts included were similar, i.e. patients with locally advanced rectal cancer who had undergone surgery at the surgical department of Karolinska University Hospital from 1991 to 2003 and 2004, respectively. The patients were referred to the Karolinska University Hospital in the Stockholm area, but also came from other regions in Sweden.

In paper III all patients were analysed with regard to residual tumour after the resections, morbidity, recurrence and survival. The prospectively reported data were collected in an internal registry and cross-checked and validated with the register from the Regional Oncological Centre and a thorough review of the medical records was also done. Deaths were confirmed by means of the Cause of Death Register. The median follow-up period was 63.5 (5–137) months.

Paper IV constitutes a comparison between the quality of life of patients with primary advanced rectal cancer and patients with primary resectable rectal cancer and also in contrast to the Swedish reference population.¹⁴¹ In paper IV, all patients from the same cohort as in paper III including one more year, 2003, who were still alive and known to be disease-free in March 2005 were contacted and asked to participate. A few of the eligible responders were found to be living with disease and were omitted from the study. All participants were asked to fill in a quality-of-life instrument on two occasions 1.5 years apart.

A reference group of patients who had undergone resection of a primary resectable rectal cancer by means of TME surgery were matched 2:1 for age, gender and time after surgery with the patients with locally advanced cancer. The reference group was asked to respond to the quality-of-life instrument on one occasion corresponding to the same period after surgery as the first occasion for the advanced patients.

Quality-of life-questionnaires

In study IV the quality-of-life instruments developed by the European Organisation for Research and Treatment of Cancer (EORTC) were used, namely, the cancer-specific core module EORTC QLQ-C30¹³⁰ and the colorectal module EORTC-CR38.¹³¹ The reason for using the EORTC QLQ-C30 questionnaire with the colorectal cancer module QLQ-CR38 in this study is that they have been widely used for patients with rectal and colon cancer although not specifically for patients with advanced rectal cancer.

EORTC QLQ-C30

The disease-specific questionnaire EORTC QLQ-C30 version 3.0 is a general core cancer-specific instrument which has been tested and continuously developed up to the current third version. The instrument has been translated into several languages, including Swedish (see appendix 1), and tested in cross-cultural settings. It has been validated and has good reliability^{130, 142-147} The questionnaire is used specifically in cancer-related measures of HRQL.

The EORTC QLQ-C30 comprises a global quality-of-life scale, five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting) and six single items evaluating different aspects of HRQL in cancer patients (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). Each item has four response alternatives, “not at all”, “a little”, “quite a bit” and “very much”, except for the global health and quality-of-life scale which has seven alternatives ranging from “very poor” to “excellent”. The time frame is the past week.

EORTC QLQ-CR38

The QLQ-CR38 module was developed to assess symptoms specific to colorectal cancer and contains four functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and eight items and symptom scales (micturition problems, chemotherapy side effects, gastrointestinal tract symptoms, male sexual problems, female sexual problems, defecation problems, stoma-related problems and weight loss). The response alternatives are the same as in the QLQ-C30. The time frame is past week or the past four weeks in the questions concerning sexuality or stoma or GI problems. In April 2007 a new version of the colorectal module was published, QLQ-CR29, in which the questions about sexuality and incontinence have been revised.¹⁴⁸

Scoring of the questionnaires¹⁴⁹

All questionnaire responses were linearly transformed to a 0 to 100 scale. A high score on the global quality-of-life scale and the function scales represents a higher level of quality of life and function, respectively, while a high score on symptom scales/items represent a higher degree of symptoms or dysfunction. Missing data were handled according to the EORTC Scoring Manual.¹⁴⁹

Interpretation of the results

Mean HRQL scores with 95% confidence intervals were calculated for the follow-up measure. Based on previous research, a difference in mean scores of at least 10 units and a non-overlapping 95% confidence interval between groups was considered to be of clinical relevance and should detect “moderate changes”.^{150, 151}

Statistical analyses

Papers I –III

The chi-square test or Fisher's exact test was used to establish the significance of differences in distributions. P values of < 0.05 were considered significant. Survival rates were estimated by the Kaplan-Meier method and the log-rank test was used for comparisons. Survival times were calculated from the day of surgery until the end of follow-up or death and, in patients without surgery, the date of the diagnosis of the primary tumour (paper I) or local recurrence (paper II) until the end of follow-up or death. Short-term complications were considered to occur within 30 days postoperatively. In paper I the impact of preoperative staging and the MDT assessment of disease-specific and overall survival was analysed in a multivariate model adjusted for age, gender and tumour level.

Paper IV

The parametric independent-by-group t-test was used to test if differences in mean scores between the total study group and the total reference group were of statistical significance at the 5% level ($p < 0.05$). The data were also analysed using the non-parametric Wilcoxon rank-sum test. As the results were fairly similar, only the results of the parametric analyses were reported.

Based on comparisons with the Swedish background population, differences in expected mean scores (population-based) and observed mean scores from the study group were tested for significance using a single sample t-test. All analyses were performed using the statistical software package Statistica® version 7-10.

RESULTS AND DISCUSSION

A comparison of patient characteristics and outcome from studies I–III is presented in table 5. The results of the respective studies will follow.

Table 5. Overview of patients and outcome in studies I- III

	Study I Primary advanced rectal cancer	Study II Locally recurrent cancer	Study III Karolinska Prim advanced rectal cancer	Study III Karolinska Locally recurrent cancer
No of patients	303	141	58	64
Median age (range)	71 (28-91)	74 (27-92)	65 (28-81)	63 (27-87)
Sex (woman/men)	138/165	58/83	22/36	29/35
Preoperative therapy				
None	147	23	1	22
RT short/long	84/34	8/9	28	10
Radiochemotherapy	31		28	31
Chemotherapy	3	1	1	1
Previous radiotherapy	4	17	0	17
Surgery	227	57	58	64
IORT	20	11	19	42
Outcome				
R0+R1	69	25	34	22
5-year survival after curative resection %	30	57	34	40
Local recurrence after curative resection	13	5	5	3

Preoperative tumour staging with multidisciplinary team assessment improves outcome in locally advanced primary rectal cancer (paper I)

A total of 303 patients with primary advanced rectal cancer were treated in 1995–2004. In the study they were divided into three groups according to the quality of their preoperative evaluation:

Group 1, local and distant staging and MDT conference (n = 69)

Group 2, local and distant staging without MDT conference (n = 99)

Group 3, not adequate local or distant staging (n = 139)

In group 1 the patients were younger (median 66) and more men were included than in the other groups. The patients were staged radiologically by MRI (98%) and CT abdomen (75%), and all had a pulmonary X-ray. The majority had an adequate TNM staging. The N stage was most difficult

to determine and 45% remained unknown. All were evaluated at MDT discussions. Preoperative treatment was given to 75%, and 82% had a resection of the tumour.

In group 2 the median age was higher (median of 68) and more women were included, although still in a minority. The radiological staging was good, but MRI and CT abdomen were used less frequently and were replaced with ERUS and abdominal ultrasound. The radiological TNM staging was good. No patients were discussed at the MDT conference. Preoperative treatment was given to 58% and the majority had short course radiotherapy, 5x5 Gy (41%). The tumour was resected in 75% of the patients.

Group 3 had a significantly older population with a median age of 76; the gender distribution was almost equal. Only 31% and 38%, respectively, were staged locally and distantly, and 15% were discussed at an MDT meeting. The radiological TNM stage remained unknown in more than 50%, and 65% received no preoperative treatment, but still 72% had a tumour resection.

Data on R0 resections, local recurrences, metastases and survival were analysed. With regard to R0 resections, a significant difference between the groups was observed: 52%, 43% and 21% in groups 1, 2 and 3, respectively ($p < 0.001$). Other factors affecting the R0 resections were type of surgery and T stage, with LAR having the highest rate (56%) of R0 resection and stage T4 a low rate (28%). Table 6 shows the crude outcome for the 165 patients resected without metastases. A macroscopic remaining tumour, R2 resection, was present in 58% with a significant difference between the groups ($p < 0.001$) with group 3 having 73% of R2 resections. Local recurrences and distant metastases were evenly distributed in the three groups; altogether, 8% of the potentially curatively resected (R0 and R1) patients suffered a local recurrence during the follow-up period. Forty-five per cent developed distant metastases. Death due to rectal cancer occurred in 55% with significantly more deaths in group 3. Overall, the estimated 5-year survival according to the Kaplan-Meyer analysis was 30% in group 1, 28% in group 2 and 12% in group 3 (fig. 12); the 5-year survival rates of the 165 resected patients without metastases were, respectively, 34%, 52% and 20% (fig. 13). In a multivariate analysis adjusted for age, gender and tumour level, the risk of death was increased in group 3 compared to group 1.

Patients with an appropriate preoperative local and distant staging received neoadjuvant treatment more frequently and had a higher rate of R0 resections than patients with preoperative staging of low quality. Cancer-specific survival was also improved. An MDT assessment enhanced adequate preoperative treatment with long-course RT or RCT and R0 resection but, in this study, could not show any effect on survival.

The population-based design with patients from all hospitals in the Stockholm-Gotland region was an advantage with regard to selection bias and increased the number of patients included. One difficulty was the lack of an ICD-10 code for the diagnosis “locally advanced primary rectal cancer”, which led to a problem in defining the population. Indirect criteria had to be used to assess the patients from the ROC registry, which may have led to an underestimation of the actual number of patients with advanced rectal cancer. However, 10% of all rectal cancer patients were found to be in an advanced stage, which is in accord with international studies in which 5–15% of rectal cancers are reported to be advanced.

A multivariate analysis of risk factors for death which could influence the preoperative treatment and subsequent surgery showed a significant risk for belonging to group 3 and aged over 70 years. Group 3, with inappropriate staging, had an older median age and involved more women, both factors analysed in the multivariate analysis. The patients in group 3 probably had a higher proportion of co-morbidity because of the more advanced age, which also could have influenced the outcome.

During the last few decades, improvements in radiological and surgical techniques and increased use of neoadjuvant RCT have occurred and may have influenced the results, but during the period 2000–2004 a third of the patients still had an inappropriate staging and only 23% of them had R0 resections.

Table 6.
Patient outcome after resection in 165 patients without metastases at the time of surgery

	Total n=165	Group1 n=44	Group2 n=44	Group3 n=77	p-value
Remaining pelvic tumour (R2)	96 (58)	16 (36)	24 (55)	56 (73)	<0.001
Local recurrence (after R0 and R1 resection)	13 (8)	3 (7)	4 (9)	6 (8)	0.286
No pelvic tumour at end of follow up	56 (34)	25 (57)	16 (36)	15 (19)	<0.001
Metastases	74 (45)	23 (52)	19 (43)	32 (42)	0.362
Rectal cancer death	91 (55)	22 (50)	20 (45)	49 (64)	0.002
Overall death	120 (73)	31 (70)	25 (57)	64 (83)	<0.001

Values in parentheses are percentages.

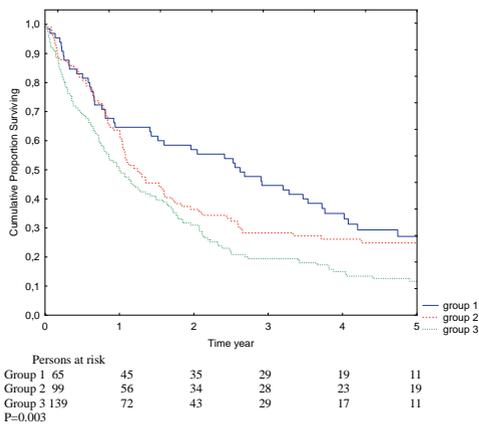


Fig. 12
Overall survival in relation to preoperative assessment in 303 patients with locally advanced primary rectal cancer

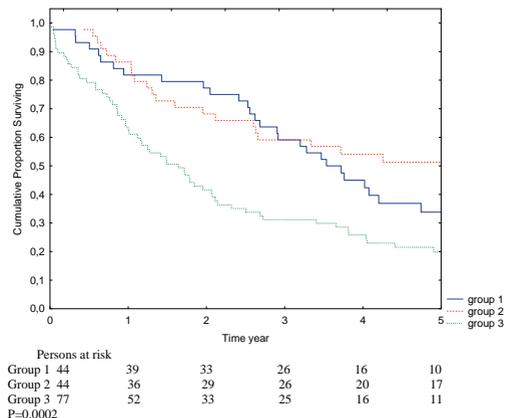


Fig. 13
Survival in relation to preoperative assessment in 165 patients without metastases resected for locally advanced primary rectal cancer

A population-based study on the management and outcome in patients with locally recurrent rectal cancer (paper II)

On comparing the patients and treatment characteristics of the 2318 patients with rectal cancer treated during 1995–2003 with the subgroup of 141 patients (6%) who developed local recurrences, no differences in age or gender were found, but a significant proportion of patients with local recurrences had not received preoperative RT (32% vs 55%; $p < 0.001$). Low tumours ($p=0.012$) and advanced tumour stage III ($p=0.001$) were also more common. At the time of diagnosis of the local recurrence 41% had disseminated disease.

Surgery was performed in 57 (40%) patients, palliative radio- and/or chemotherapy was given to 48 (34%) and 36 (26%) received only symptom palliation.

Among the patients treated with surgery, 30% received preoperative RT, 30% were irradiated before the primary operation and 40% had no preoperative treatment. In seven patients, only an explorative laparotomy was performed without resection of the recurrence. Six patients were found to have disseminated disease at surgery. A curative resection was achieved in 25 patients (44%). The surgery was associated with a high morbidity, with only one third without postoperative complications.

Overall survival in all patients with local recurrences was 9% at five years. In patients having a potentially curative resection, the estimated 5-year survival rate was 57%. After palliative RT, the median survival time was 12 months (3–60) and, for symptomatic palliation, 3 months (0–29). Survival in relation to treatment is shown in figs. 14 and in relation to radicality of surgery in fig. 15. Seven of 25 potentially curatively resected patients suffered recurrent disease, one with only a local recurrence and four with combined pelvic and distant disease.

Table 7 shows a comparison with a previous study in the Stockholm region during 1980–91.¹² A noteworthy finding was the decreased incidence of local recurrences from 23% to 6%. Curative resections were achieved in 25 of 57 cases, compared to 12 of 72 in the previous study and the estimated 5-year survival after curative resection had increased from 42% to 57% and the overall survival also showed an increase.

The introduction of TME technique with improved surgery and preoperative RT has significantly reduced the incidence of local recurrences.^{1,3,4,9} This study illustrated quite well the improvement over time in comparison with the previous study conducted 12 years earlier.¹² The only possibility for cure is complete removal of the recurrence. RCT can only offer a temporary palliation as shown by a median survival of 12 months.

Risk factors for local recurrences in this study were surgery without preoperative RT, low tumour, surgery with local excision and tumour stage III. Only one third of the patients had received RT before the primary surgical event and less than half of them were irradiated before surgery on the recurrences. This indicates a suboptimal use in the area of RT.

The proportion of local recurrences judged to be resectable tumours had not increased over time and only two out of three were evaluated preoperatively by MRI before surgery and 11 out of 57 patients were found to have metastases at surgery, which could indicate a need for a more proper preoperative evaluation of this patient group.

In this study patients with local recurrences had disseminated disease in 43% of cases and only 40% underwent surgery with a curative intent owing either to old age or being found to be inoperable after radiology. In conclusion, it seems important that all local recurrences should be discussed at an MDT conference to allow a careful selection of patients with local recurrences who would benefit from surgery.¹¹⁰

Table 7.

Comparison of data with a study of 156 local recurrences 1980-1991* and 141 local recurrences 1995-2005.

Study years	1980-1991	1995-2005
Total "curatively" operated	684	2318
Preoperative radiotherapy	337 (49)	1257 (55)
Local recurrences	156 (23)	141 (6)
Mean age at primary surgery (years)	65	71
Surgery for recurrence	72 (46)	57 (40)
Chemo-RT only	44 (28)	48 (34)
Symptomatic	40 (26)	36 (26)
5-years survival total	4 %	9 %
Surgery		
Curative	12/72 (17)	25/57 (44)
5 year survival after curative surgery	42 %	57 %
Re-recurrence	4/12 (33)	5/25 (20)

Values in parenthesis are percentage

* Holm T, Cedermark B, Rutqvist LE. Local recurrence of rectal adenocarcinoma after 'curative' surgery with and without preoperative radiotherapy. *Br J Surg* 1994;**81**:452-5.

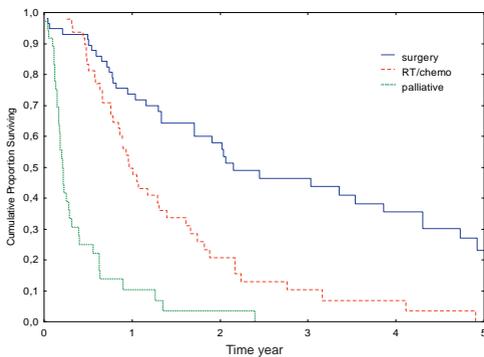


Fig. 14
Overall survival in relation to treatment in 141 patients with local recurrent rectal cancer.

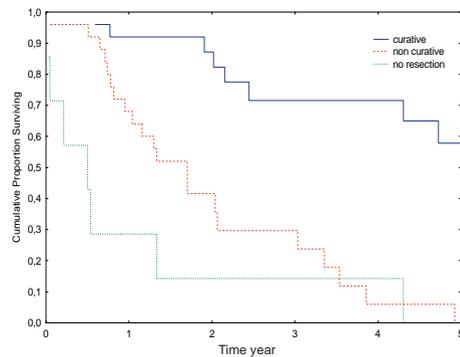


Fig. 15
Overall survival in 57 surgical treated patients in relation to curative, uncertain or non-curative surgery

Outcome after the introduction of a multimodality treatment programme for locally advanced rectal cancer (paper III)

Fifty-eight of 122 patients with locally advanced rectal cancer had primary rectal cancer and 64 had local recurrences of rectal cancer. All but one patient with primary rectal cancer had had preoperative RT or RCT. One third of the patients with recurrent disease had no preoperative treatment and 77% of them had previously received RT before surgery on their primary tumour. Distant metastases were found in 10 patients with local recurrences and they were operated on for palliative reasons. APR predominated as the surgical procedure in both primary advanced rectal cancer and locally recurrent cancer. Pelvic exenterations were performed in 15 of 58 of the primary advanced rectal cancer patients and only in 6 of 64 patients with recurrent disease. IORT was given to 61 patients, 19 with primary cancer and 42 with recurrent disease. Curative resections were achieved in 34 patients with primary cancer and in 22 patients with local recurrences.

Both groups of patients had a high rate of early postoperative complications, such as wound infections, wound dehiscence and abscesses and postoperative urinary or pulmonary infections. Only 18% had no long-term complications, and the complications ranged from mictural and gastrointestinal disturbances to fistulas. Thirty per cent of the patients complained of persistent pain.

Thirty-four of the 58 patients with primary advanced rectal cancer had a potentially curative resection, and five of these developed local recurrences. Twenty-two of the 48 patients with locally recurrent rectal cancer were resected curatively and 3 suffered a local recurrence. The five-year survival for curatively resected and non-curatively resected patients is presented in fig. 16.

This study on the introduction of MDT of patients with locally advanced rectal cancer, including primary advanced rectal cancer and local recurrences, showed the importance of achieving a curative resection. With curative surgery, the risks of local recurrences and of survival were similar regardless of the diagnosis. However, the rate of potentially curative resections was significantly higher in patients with primary advanced rectal cancer. The surgery of local recurrent rectal cancer is considered to be more demanding as a resection in the pelvis has already been performed and the mesorectum should have been removed. However, in a recent study of locally recurrent cancer, Syk et al. reported radiological suspicions of a remaining mesorectum in patients with locally recurrent disease.¹³ Moreover, the patients with primary advanced rectal cancer had received preoperative RT more often, with a subsequent downsizing in 70% of the tumours, which may have enhanced the possibility of a curative resection. During the period 1991–2002 an increased awareness of the importance of careful preoperative evaluation and staging in these patients persisted. Also running was a trial (LARCS) that randomised patients with advanced rectal cancer to preoperative RT or RCT, resulting in only RT to 48% of the patients. Yet, today, RCT is recommended for improved downstaging and local control.^{58,59} Early in the study period, more patients underwent surgery for locally recurrent cancer. The introduction of TME surgery and preoperative radiotherapy in the 1990s led to a drastic decrease in local recurrences from 15% to 6% in the Stockholm region.³ Therefore, in the latter part of the study, the majority of patients had primary advanced rectal cancer. Another factor of importance to this might be the improved local staging with better determinations of radiological T4 tumours by phased array MRI.

Despite the improved rate of curative resections, the majority of the patients still got postoperative and long-term complications, which raised the question of quality of life in resected patients (paper IV).

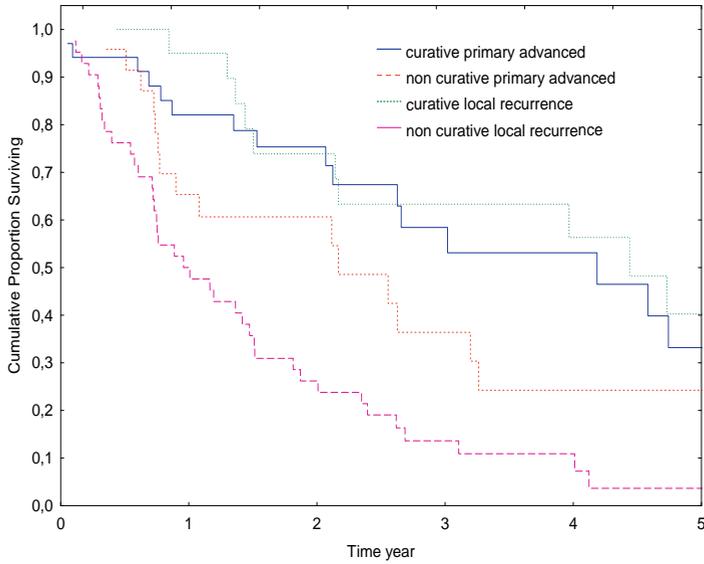


Fig. 16

Estimated survival for patients resected with locally advanced rectal cancer at Karolinska University hospital 1991-2002

Quality of life after potentially curative treatment for locally advanced rectal cancer (paper IV)

The EORTC QLQ-C30 and CR38 were answered by 43 patients operated on for advanced rectal and 80 reference patients operated on for primary resectable rectal cancer. All but four of the patients with advanced cancer had received preoperative RT, compared to 76% of the patient in the reference group. Thirty-five patients had had en bloc resections of other organs and 37 out of 43 ended up with a permanent stoma. A urostoma was present in nine patients and two had received an orthotopic bladder. In the reference group, 20 patients had got a stoma after APR or Hartmann's resection, and two had a remaining diverting ileostomy. The majority of the study patients had a T4 tumour or a local recurrence, while T2 and T3 were predominant in the reference group.

A comparison in the EORTC QLQ-C30 between the study group and the reference group is shown in table 8. The mean scores on role, social and physical functioning and the global quality of life were significantly lower in patients with advanced disease, as the symptoms pain and fatigue were more predominant in this group. On repeating the inquiry 1.5 years later in 36 patients, no significant differences were found. A gender difference was noted as women reported a better quality of life, role and social functioning, and less pain and fatigue than men.

In the colorectal module EORTC QLQ-CR38, the functions of body image and defecation problems were evaluated lower in the study group (table 9).

In addition, in relation to the Swedish background population, the study group reported significantly lower scores both clinically and statistically on the global quality of life and physical, role and social functioning.

Patients treated for locally advanced rectal cancer with preoperative RCT and extensive surgery scored lower than patients in the reference group on almost all functions, but the differences were relatively small. A Norwegian study on a similar patient group has shown no difference in the quality of life compared to a reference group of rectal cancer patients and the Norwegian population with a similar follow-up period after surgery.¹⁵² Several studies and Cochrane analyses of the impact of a stoma on body image and quality of life have been conducted, but no consensus was reached.^{127, 138, 153} In the present study the patients with stoma reported reduced body-image perception, which could also influence the role and physical functioning.

The observed gender difference in favour of women was unexpected as other studies have reported a better HRQL in men.^{141, 154} In the present study men had a higher rate of pelvic exenterations and were living with two stomas, which could have influenced the scoring.

Functional problems, such as impaired bowel function, incontinence and urinary problems in rectal cancer patients may also influence the long-term HRQL. However, some of these symptoms may diminish with time and the patient will adapt to a lower state of function. In this study no significant changes over time were noted when the patients re-evaluated their HRQL after 1.5 years, but a trend towards improved functioning was seen. Since the time after surgery varied over a broad range in the study, the expected improvement, which is seen most often within 1-1.5 years after surgery, was not demonstrated.

In conclusion, potentially curatively treated patients with locally advanced rectal cancer evaluated their HRQL as impaired compared to patients treated for primarily resectable rectal cancer and compared to the general Swedish population. The importance of good preoperative information and counselling and of postoperative care should be stressed among caregivers of patients with locally advanced rectal cancer.

Table 8.
EORTC QLQ-C30 in patients after extended surgery for advanced rectal cancer (study group) compared to patients after total mesorectum excision (reference group) presented as mean scores with 95% confidence intervals (CI).

	Study group Mean score (95%CI)			Reference group Mean score (95% CI)			p-value*
	Female n=21	Male n=22	Total n=43	Female n=41	Male n=39	Total n=80	
Overall**							
Global health status	64 (53-75)	55 (43-67)	60 (52-68)	70 (63-78)	68 (59-76)	69 (63-74)	0.05
Functions**							
Physical	74 (62-66)	71 (60-82)	72 (64-80)	82 (75-88)	81 (73-88)	81 (76-86)	0.04
Role	66 (50-82)	56 (39-73)	61 (49-72)	82 (74-89)	74 (63-84)	78 (72-84)	0.00
Emotional	80 (72-88)	77 (65-88)	79 (72-85)	81 (74-87)	80 (73-88)	81 (76-85)	0.64
Cognitive	86 (77-95)	75 (66-85)	80 (74-87)	84 (77-91)	85 (79-91)	85 (80-85)	0.30
Social	73 (62-85)	54 (40-68)	63 (54-73)	81 (72-90)	77 (68-87)	79 (73-85)	0.01
Symptoms***							
Fatigue	29 (18-40)	41 (29-54)	35 (27-44)	23 (16-31)	26 (18-34)	25 (19-30)	0.03
Nausea and vomiting	6 (-1-13)	10 (1-20)	8 (3-14)	4 (0- 7)	5 (0- 9)	4 (1- 7)	0.16
Pain	25 (13-37)	28 (14-42)	27 (17-36)	17 (10-24)	19 (11-27)	18 (13-23)	0.09
Appetite loss	7 (-1-15)	18 (4-32)	13 (4-21)	8 (3-13)	7 (1-13)	8 (3-11)	0.21
Constipation	3 (-1- 8)	11 (1-20)	7 (2-13)	12 (4-20)	18 (7-28)	15 (9-21)	0.11
Diarrhea	32 (13-50)	29 (15-42)	30 (19-41)	28 (17-39)	21 (13-30)	25 (18-32)	0.40

*Independent t-test was used to calculate the statistical significians at the 5% level between the total mean in the study group and reference group.

**Score range from 0-100, a high score represents a better level of quality of life and function.

***Score range from 0-100, a high score represents more severe symptoms.

Table 9.
EORTC QLQ-CR38 in patients after extended surgery for advanced rectal cancer (study group) compared to patients after total mesorectum excision (reference group) presented as mean scores with 95% confidence intervals (CI).

	Study group Mean score (95%CI)			Reference group Mean score (95% CI)			p-value*
	Female n=21	Male n=22	Total n=43	Female n=41	Male n=39	Total n=80	
Function**							
Body image	58 (44-73)	51 (37-66)	55 (45-64)	76 (67-85)	82 (74-90)	79 (73-85)	0.00
Future perspective	62 (46-77)	65 (49-81)	64 (53-74)	63 (53-73)	69 (61-78)	66 (60-73)	0.66
Symptoms***							
Micturition problems	29 (16-42)	30 (20-40)	29 (21-37)	28 (22-34)	28 (23-34)	28 (24-32)	0.75
Gastrointestinal	16 (11-22)	17 (10-24)	17 (12-21)	22 (17-27)	17 (13-22)	20 (12-21)	0.26
Defecation problem	13(-23-48)	16 (-2-33)	14 (3-25)	25 (20-31)	30 (23-36)	27 (23-31)	0.06
Stoma-related problem	34 (22-46)	37 (26-48)	36 (28-43)	47 (10-84)	23 (11-36)	30 (18-43)	0.43
Weight loss	11 (-1-23)	8 (0-15)	9 (2-16)	14 (7-20)	10 (3-17)	12 (7-17)	0.50

*Independent t-test was used to calculate the statistical significians at the 5% level between the total mean in the study group and reference group.

**Score range from 0-100, a high score represents a better level of quality of life and function.

***Score range from 0-100, a high score represents more severe symptoms.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Design

Studies I–III, in the present thesis were observational studies, with retrospective cohorts of patients with locally advanced rectal cancer, in which prospectively recorded register data were analysed. Additional data were retrieved from medical case records. Study IV was a prospective study of HRQL in a retrospective cohort.

The low incidence of locally advanced rectal cancer makes a randomised study design difficult. The observational study design makes it possible to study various factors simultaneously concerning the management of patients with advanced rectal cancer. Some advantages of a retrospective cohort study are the possibility to a longer follow-up and that they are less costly, but a disadvantage is that they have to rely on existing records with the risk of missing information. The statistical power in all four studies is low because of the low incidence, which is a common problem in most studies of locally advanced rectal cancer even at large specialised centres.

One strength of studies I–II was that they were population-based, which decreased the selection bias and increased the eligible number of patients. Studies III–IV were hospital-based studies, but the material was collected by a surgeon not involved in the treatment of the patients studied, which should decrease the risk of selection bias.

Sweden is unique in having national social security numbers and national registers such as the Inpatient Register, Cancer Register, Death Register and the Population Register. This provides an opportunity to do reliable research on registry data. In studies I–III the Regional Colorectal Cancer Registry from the ROC in Stockholm was used. This registry is based on reports from surgeons, oncologists and pathologists, and the registration is done by a data manager who also enforces the collection of data. The registry is continuously validated and cross-checked with the above-mentioned registries and checks on medical records. Several previous research projects have added to the validation of the register.

However, the problem of incomplete reports still exists, especially concerning local recurrences. There is no general agreement on a follow-up program for rectal cancer patients in the Stockholm region, although most surgical departments follow their patients regularly for at least three years. The Swedish National Colorectal Registry will soon launch guidelines for a minimum surveillance and an ongoing European multicentre study, COLOFOL, randomises between a minimum follow-up and a high-frequency follow-up for colorectal cancer patients. Most recurrences occur within 2–3 years,¹⁵⁵ but if the patients are not followed up at a surgical or oncological clinic, recurrences may be missed and not reported. Commonly, if the patients are found to have disseminated disease, a follow-up for local failure is often omitted. In study II in the present thesis, the incidence of local recurrences was found to be 7%, which could constitute an underestimation.

As mentioned before, the definition of primary locally advanced rectal cancer is unclear, which can also lead to an under- or overestimation, depending on the surgeons' conception of locally advanced rectal cancer.

Management

Preoperative tumour staging

The study periods in the present thesis ranged from 1991 to 2004. The value of preoperative RT in rectal cancer surgery was assessed in the Stockholm I and II studies, during 1980–93, which showed a reduced frequency of local recurrences after RT.^{1, 5} The concept of TME surgery was introduced in the Stockholm region by workshops at the beginning of 1994 and an evaluation in 2000 showed an additional remarkable decrease in local recurrences.³ The methods for preoperative tumour staging have changed and improved over the period. The refined MRI with phased array coils and high resolution have increased the accuracy in determining the tumour in relation to CRM.^{22, 23} The increased availability of PET/CT will further improve the distant staging and detection of local recurrences. According to regional guidelines, appropriate local and distant staging is recommended with an emphasis on staging for locally advanced rectal cancer.

T4 rectal cancer growing outside the mesorectal fascia with lymph node assessment in proximity to the mesorectal fascia, as evaluated by ERUS, has been shown to have a low accuracy and overstaging is frequent.^{25, 156} The accuracy of local staging with ERUS was only 69% compared to 98% with MRI in a study of patients with locally advanced rectal cancer by Brown.²³ The recommended method for local staging of advanced rectal cancer should be MRI.

In the present thesis, study I dealt with the importance of assessing the tumour stage before surgery in patients with locally advanced primary rectal cancer. In the study, the outcome after an appropriate preoperative staging was improved with regard to radicality of surgery, local control and survival. MDT discussions further improved the frequency of adequate preoperative treatment and the rate of R0 resections.

Before 2000 MRI was used infrequently at most hospitals in the Stockholm region, except in the Karolinska University Hospital. Even if the patients were evaluated by MRI, the quality of the examination or the interpretation of the images was often suboptimal.³¹ Recently, several studies and workshops have discussed the training for MRI interpretations of rectal cancer and the role of MRI in MDT discussions for enabling an improved selection of patients and evaluating risk factors for preoperative treatment and surgery.^{25, 32, 41} In study I about two thirds of the patients with locally advanced primary rectal cancer had been evaluated preoperatively by MRI, but only one third in group 3 were locally staged, which was reflected in the outcome. In some patients, the local staging was done with only ERUS. MRI was used for local staging more frequently at the university hospital (study III) compared to the other hospitals in the region (studies I and II).

PET will probably have increased importance for the detection of local recurrences in the future. One disadvantage of MRI is the difficulty to distinguish tumour from fibrosis and subsequently from postoperative scar tissue. An early local recurrence is difficult to diagnose on MRI; meanwhile, PET will more readily detect tumour tissue.¹⁵⁷⁻¹⁵⁹ During the period of time for studies II and III, which dealt with local recurrences, PET/CT was not used in clinical practice; therefore these studies could not evaluate the use PET/CT. For distant staging, local traditions are predominant in deciding on CT thorax/CT abdomen/ultrasound abdomen/chest X-ray. Contrast-enhanced ultrasound of the liver has been shown to have higher sensitivity and specificity for liver metastases than conventional ultrasound.¹⁶⁰

Preoperative treatment

Preoperative treatment of locally advanced rectal cancer with RCT or long-course RT (40-50 Gy) has been recommended mostly because of their downsizing and down-staging effect, but without evidence of an improved outcome until some recent studies demonstrated the benefit of RCT. Gerard et al. and Bousset et al. demonstrated improved local control and Braendengen et al. could also present prolonged cancer-specific survival and time to failure in the LARC study.⁵⁸⁻⁶⁰

In the population-based studies in this thesis, less than 30% of patients with locally advanced rectal cancer had RCT or long-course course preoperative RT, in contrast to the University hospital where two thirds had long-course RT or RCT. These results indicate undertreatment of the patients with locally advanced rectal cancer. The University hospital had regular MDT discussions of all rectal cancer patients under this period and had a significantly higher percentage of preoperative treatment. Other influential factors could be the availability of RT in the region at the time, but there was no difference for the different hospitals except that the surgery department at the University hospital was in close proximity to the RT unit. Patient compliance with and acceptance of RT could also differ, especially if some hospitals in the region had an elderly population.

All patients are not fit for RCT, especially the elderly, with co-morbidity such as cardiovascular disease. It is important to discuss this patient group at MDT meetings in order to individualise their treatment. Short-course RT with delayed surgery has been shown to be a promising alternative in a small single-centre study.⁶³ The patients, all with primary unresectable rectal cancers and contraindications to RCT, experienced a substantial downstaging effect of 5x5 Gy with a low toxicity. The approach with short-course RT and delayed surgery is currently being evaluated in a randomised trial in patient with primary resectable rectal cancer (Stockholm III).

Patients with local recurrences who have been irradiated previously for the primary rectal cancer have usually not been re-irradiated. The possibility of re-irradiating is dependent on the maximum tolerable dose to the tissue and the interval of time from the previous RT. The small intestine is more radiosensitive than other tissue in the pelvis. The preoperative radiation dose is about 70% of the maximum tolerable dose if the small intestine can be excluded from the irradiation field.^{161, 162} A study from the Mayo Clinic on irradiated patients with local recurrences showed good acceptance of IORT and, in a subgroup, an addition of RT 30 Gy. The local control was higher in the subgroup with additional RT, but long-term survival was poor because of distant metastases.¹⁶³

The clinical nature of rectal recurrences may be more aggressive after preoperative RT. In a Dutch study, the majority of irradiated patients with local recurrences had simultaneous distant metastases and a shorter median survival than the non-irradiated group.¹⁶⁴

Surgery

To achieve a cure in a patients with primary advanced or recurrent rectal cancer, a complete surgical removal is mandatory.^{71, 95, 165-171} An extended TME or en bloc resection of neighbouring organs is necessary to enable a radical resection. Only patients with an R0 resection have considerable long-term survivals. In studies I and III pertaining to patients with primary advanced rectal cancer, the rates of curative resection were 35% and 59%, respectively. Patients with local recurrences were radically resected in 44% of cases in study II, compared to 40% in study III. On comparing the rates of radical resections from the different hospitals in study I, more than half came from the university hospital. There was a wide range of rates of R0 resections in the different hospitals, but the individual volumes were too low to allow statistical calculations. The proportion of patients with local recurrences suitable for resections had not increased in comparison with a historical study, in spite of refined evaluation and surgical methods.¹²

In international studies the reported R0 resection rates have generally been higher.^{14, 76, 109, 112, 170, 172, 173} All of these studies were from dedicated single centres with a great experience of patients with locally advanced rectal cancer.

A disputable question is the resection planes after preoperative treatment. The difficulty to distinguish between tumour tissue and fibrosis on MRI is troublesome when determining the plane of resection. As already discussed in this thesis, at the Karolinska University hospital we plan the surgery planes based on the primary extension of the tumour as shown at the initial MRI. An unpublished histo-pathological study from our department showed remaining tumour cells in the fibrotic tissue after RT, which supports this strategy. Several studies on the accuracy of MRI after RCT or long-course RT have shown a decreased accuracy in determining the radiological TNM stage compared to the primary MRI.¹⁷⁴⁻¹⁷⁶ A small study from the Karolinska University hospital evaluated the importance of the second MRI in changing the primary decision concerning tumour invasion in locally advanced rectal tumours. The result was that the initial interpretation was not changed.³⁰

A partial regression of tumour after preoperative RCT can still have lymph node involvement indicating an aggressive potential of the malignant cells and justifying a more extended excision plane.¹⁷⁷

The surgical resection and reconstruction often requires a multidisciplinary approach, which has to be planned before surgery. Several studies have demonstrated the importance of case volume for the individual surgeon with regard to rectal cancer and, for locally advanced rectal cancer, this should be even more important.^{92, 178} The centralisation of the surgery of locally advanced rectal cancer facilitates an optimal management of the patients. In Stockholm, the surgery of locally advanced rectal cancer was gradually centralised during the study period, but only in the last third of the period was a notable increase in patient load seen at the Karolinska University Hospital.

Histopathology

Important prognostic factors for rectal cancer survival are T stage, N stage and M stage, but also vascular invasion, perineural growth, residual stage and circumferential margin are significant risk factors.^{38, 106, 108} The demand for high-quality pathology reports has increased. During the period of the preparation of this thesis, there has developed an increased awareness of the importance of good histopathology, both for predicting survival and for adjuvant therapy and as a quality factor in surgery. In the pathology reports from the first half of the study period, the total number of lymph nodes examined, the circumferential margin and vascular and perineural invasion were infrequently mentioned. Although the quality has improved, more work remains to be done to achieve a standardised evaluation of tumour specimens.

Some discrepancy still exists, in judging the differentiation between T3 and T4 tumours with regard to growth outside the mesorectal fascia or the necessity to demonstrate cancer growth into neighbouring organs. In the studies in this thesis, patients with non-radical T3 tumours are included when the surgeon concluded that there was macroscopic tumour growth outside the mesorectal fascia but the histopathology is described as T3 R1.

In colon cancer nodal stage is important in determining if the patients will benefit from adjuvant chemotherapy as stage III colon cancer has shown a 10–12% gain in 5-year survival with adjuvant 5-fluorouracil-based chemotherapy.^{42, 179} In rectal cancer the advantage of adjuvant therapy has not been proven and most adjuvant therapy is given in studies (the SCRIPT study). Also the number of harvested lymph nodes is of importance as a prognostic factor in colon cancer. The total number of lymph nodes will be a factor in the quality of the resection and in the histopathology but it has also been shown to be an independent factor for outcome.¹⁸⁰⁻¹⁸² In the specimen after surgery for locally advanced rectal cancer, the lymph nodes have been affected by the preoperative RCT and are often

necrotic in appearance and more difficult to define. A recently published Dutch study of prognostic factors after RCT showed that the local recurrence rate and the overall survival rate decreased with the number of lymph nodes involved.¹⁰² However, in the same study the strongest predictor of local recurrences and survival was CRM involvement. A Chinese study has shown the prognostic importance of metastatic lymph node ratio also in rectal cancer.¹⁸³

The importance of CRM as a prognostic factor in rectal cancer has attracted more attention than the number of lymph nodes in rectal cancer research.^{37, 178} A positive CRM can be defined as the histological identification of tumour within 1 mm of the surgical resection margin¹⁸⁴ and it correlates with an increased incidence of local recurrences, systemic failure and poor survival.³⁷

In the near future, tumour genetic markers such as KRAS will be important for determinations in adjuvant target monoclonal antibody therapy. Recent research has shown that wild-type KRAS was required but was not sufficient to confer sensitivity to anti-epidermal growth factor receptor (EGFR) antibody as panitumumab monotherapy in treating liver metastases of colorectal cancer while mutant KRAS was resistant to anti-EGFR antibody therapy.^{185, 186}

MDT

The impact of MDT meetings has been debated. A meaningful MDT conference concerning rectal cancer patients should include a colorectal surgeon, an oncologist, a radiologist, a pathologist and a specialised contact nurse. The team should discuss treatment strategies for preoperative evaluation, optimal neoadjuvant treatment and surgical resection planes with the intention to individualise and optimise the management of the patient. Some surgeons argue that MDT meetings are a waste of time and straight communication with colleagues leads to the same care of the patient. However, the treatment of advanced rectal cancer is demanding and has a high morbidity. It is of the utmost importance to evaluate the advantages and disadvantages of the proposed treatment for each patient, also considering the co-morbidity and social situation of the patient. The MDT meeting also serves as a quality control of radiology and histopathology. At the Karolinska University Hospital colorectal MDT meetings have a long tradition and are well functioning. For a couple of years now, other hospitals have had the opportunity to join the meeting by telecommunication.

Few studies have evaluated the function of MDT discussions. In study I, the impact of MDT meetings concerning patients with advanced rectal cancer resulted in an increased number of patients receiving neoadjuvant treatment and more R0 resections were achieved in patients discussed at MDT meetings compared to appropriately preoperatively evaluated patients without MDT discussions. A British study on the introduction of mandatory MRI-based MDT of patients with rectal cancer resulted in reduced positive CRM to 1% of resected patients compared to 26% in a comparable group of non-MDT-discussed patients.⁴⁵ A recent Swedish study demonstrated more aggressive treatment of liver metastases in colon cancer patients after MDT.⁴⁶

Outcome

Recurrence

In study I the rate of local recurrences after an R0 resection was 8%. The rate did not differ between the treatment groups, which was an expected result as the major factor for remaining local disease free has been shown to be a radical resection. However, a significant difference was noted between the three groups concerning the rate of remaining pelvic tumour after surgery (R2). In group 1,

with appropriate preoperative evaluation and MDT discussion, 36% were R2 compared to group 3 without proper evaluation where 73% had an R2 resection. In study III the local recurrence rate was 15% in patients with primary rectal cancer. The higher rate can be explained by the small size of the study but also by the earlier study period starting already in 1991 when more recent improvements in management were not yet available. In international studies, the local recurrence rates after advanced rectal cancer ranges from 7% to 31%.^{72, 102, 187-189}

The diagnosis and definition of local recurrence may vary as discussed earlier in this thesis, which could influence the reported rate. According to study II, most local recurrences occur within 2 years. As one third were discovered at routine follow-ups, a regular surveillance programme would be indicated for rectal cancer patients.

Surgery for local recurrences has a higher risk of re-recurrence with rates of 20–35% within 3–5 years, a rate similar to that shown in studies II and III.^{14, 75, 110, 166} Studies analysing risk factors for local recurrence have shown that lymph node involvement and CRM positivity have increased the risk of local recurrences.^{102, 177}

Risk factors for a re-recurrence were shown to be a positive CRM and the degree of fixation of the local recurrences in the pelvis in a study from the Mayo Clinic.¹⁵ Garcia-Aguilar considered that tumours that re-recr locally without distant metastases may be of a different biological nature.¹⁶⁶ Several centres use IORT especially in the surgery of local recurrences with promising results, but other centres have not been able to show any outcome benefits of IORT.^{78, 190-193} No randomised studies have been done.

Survival

A prerequisite for survival is a potentially curative resection of the primary tumour or recurrences. In all three studies pertaining to outcome after surgery, patients who have undergone R0 resections have a promising estimated 5-year survival of 34–57%, while non-curatively resected patients do not survive five years. Other recent studies on patients with locally advanced rectal cancer treated in the last 15 years have shown a better 5-year survival of around 50–60%.^{14, 76, 172} The lower survival rate in our studies may be due to the population-based patient material with several hospitals involved without an optimal multidisciplinary approach. Also the low frequency of preoperative treatment should have influenced the outcome.

RCT leads to different degrees of tumour regression from no sign of regression to a complete response in 10–20%.^{81, 177, 194} A recent Dutch study evaluating factors determining outcome after RCT showed that tumour regression is more pronounced after RCT than after only long-course RT.¹⁰² RCT cannot compensate for bad surgery. Radical excision with a negative CRM was essential for local control and improved survival. The rate of tumour-free circumferential margin was improved after neoadjuvant therapy. After total tumour regression, some patients still had lymph node involvement.

Survival after advanced rectal cancer has been shown to be dependent on resections with tumour-free circumferential margins, R0 resection and nodal status.¹⁰²

QoL

The quality of life is important for these surviving patients. HRQL has gained increasing importance as an outcome factor after treating patients with cancer.^{126, 153, 195} An awareness of other factors such as the patients' physical, cognitive and emotional functioning after complicated preoperative

treatments and mutilating surgery is necessary for counselling. Patients with locally advanced rectal cancer have a long and difficult preoperative evaluation and treatment with RCT accompanied by emotional worries about the outcome of the treatment, followed by extensive surgery, often with complications, and ending up with remaining gastrointestinal dysfunction or stomas. Afterwards they live in fear of recurrences or distant metastases.

In study IV the HRQL of disease-free patients after surgery for primary locally advanced rectal cancer or recurrent rectal cancer was evaluated. The cancer-specific questionnaire EORTC QLQ-C30 and its colorectal module QLQ-CR38 were used.^{130, 131} These questionnaires are frequently used and validated in HRQL studies and are easy to administer. Several aspects of HRQL were impaired, e.g. physical, role and social-functioning and global health. The patients scored the function of body image low and the symptom of pain and fatigue high in comparison with the reference group with primary resectable rectal cancer. Aspects concerning sex frequently were not answered; also questions concerning GI problems had a low answering frequency, probably because of stomas in many patients. This led to exclusions in the analysis of the questions concerning sex. It would be helpful to inform the patients about changes in HRQL after treatment in the preoperative information. Other studies have shown a return to baseline in HRQL in patients with rectal cancer after one year postoperatively.^{196, 197} As the period after surgery varied for the patients, we could not analyse changes over time. A second questionnaire after 1.5 years revealed a trend to improvements, but no significant changes were noted. If the anxiety about relapse fades, social and emotional functioning may improve.

The patients scored high on the symptoms pain and fatigue, which were long-term complication also noted in study III. Pain after RT and extensive surgery could depend on nerve damage and scar tissue in the pelvic region. After reconstruction with gluteal flaps, some patients notice a change in sensitivity in the perineum, which could be perceived as inconvenient. However, the symptoms may diminish with time and the patient may adapt to a lower state of function and value other factors in life, i.e. a so-called “response shift” may occur.^{129, 198}

The impact of living with a stoma on HRQL has been debated and a Cochrane analysis of studies on the issue could not draw any conclusions.¹³⁸ In the study, 86% of the patients were living with one or two stomas. Having a stoma certainly affects the perceived body image and low scores on such items as role, physical and social functions could at least be partly due to problems and discomfort with the stoma.

Gender

Rectal cancer is more common in men than in women for unknown reasons. Also in this thesis, men were overrepresented in both the population-based studies on primary rectal cancer and local recurrences, and in the single-centre study. Analyses of management in the studies showed a gender difference.

With regard to preoperative assessment in study 1, group 1 with appropriate preoperative treatment and MDT discussions, included 38% women and group 3, with inappropriate evaluation, had 49% women compared to 46% women in total in the study. Preoperative treatment with long-term RT or RTC was given to 31% of the men and only 18% of the women. Even in group 1, men received adequate treatment more often (81% vs 62%). Outcome in terms of R0 resections did not differ in total, although in group 1 men had 43% R0 resections while women had 62%.

In study II, 86% of the women received no preoperative treatment in comparison with 60% of the men. Nevertheless, the rate of R0 resections was higher in woman. In study III from Karolinska University Hospital, the inequality of received preoperative treatment persisted with 73% of the women and 65% of the men, receiving long-term RT or RCT.

In spite of the preoperative undertreatment of women, they rated their postoperative HRQL better than men did in study IV. The study could not identify factors that explained the worse outcome in men.

In conclusion, there are differences in the treatment, but they are not obvious in the outcome. The differences are hard to explain. There seems to be other factors than age and gender which influence the treatment decisions. Co-morbidity, for example, was not studied in this thesis. The gender aspects need to be studied further. In a national survey of gender differences in the treatment of rectal cancer in Sweden, similar results were found with men receiving more frequent preoperative RT without any plausible explanation, and no outcome gain was observed.¹⁹⁹

Future perspectives

With the increased centralisation of patients with locally advanced rectal cancer, the population-based results from the Stockholm region will probably improve. Hopefully, in the near future, all patients will be evaluated preoperatively both locally and distantly by means of radiology of good quality, followed by MDT discussions to plan an individualised optimal preoperative treatment. Surgery should be offered at specialised centres with the possibility of a multidisciplinary approach. The histopathology assessments should be standardised and support the decision regarding adjuvant therapy. Postoperative surveillance will detect local recurrences in an early stage.

Regular conferences and meetings with discussions of these issues will continue to increase the awareness of good management and evaluation of patients with rectal cancer.

Despite improved staging and preoperative treatment with improved local control after surgery, almost 50% of the patients still get distant metastases. An increased frequency of surgical resection of liver and lung metastases is necessary. A population-based study in the Stockholm area on patients with liver metastases after colon cancer showed that only 4% had had a surgical resection.²⁰⁰ New therapeutic agents for adjuvant chemotherapies such as targeted antibodies have shown promising results in treating both the primary rectal tumour and liver metastases.²⁰¹

With improved survival after long-term preoperative treatment and extensive surgery with high morbidity, the concern for an acceptable quality of life for these patients is raised. A prospective study of HRQL in all treated patients with rectal cancer has been initiated. Also in the postoperative clinical setting, the QoL questionnaires could be used to find patients with impaired functioning and give them adequate care and support within the colorectal unit as well as psychosocial counselling. It would be interesting to evaluate whether the observed gender difference in HRQL still persist in a prospective study. The underlying factors for the observed lower HRQL could become evident in a prospective follow-up of the quality of life.

CONCLUSION

Overall conclusion

Patients with locally advanced rectal cancer have severe symptoms. An appropriate preoperative evaluation is a prerequisite for deciding on adequate neoadjuvant treatment followed by optimised, potentially curative surgery. About 50% of the patients may be cured after extensive surgery. The tumour-free patients have a slightly impaired quality of life, but this may be an acceptable condition if the alternative is long-term suffering and death from cancer.

Specific conclusions

- Preoperative radiological tumour staging in patients with locally advanced primary rectal cancer increases the proportion of neoadjuvant treatments and the rate of potentially curative resections with improved local control and survival.
- MDT discussions of patients with locally advanced primary rectal cancer lead to higher rates of curative resection and improved local control.
- After a complete resection of locally recurrent rectal cancer, more than half of the patients may be cured.
- The introduction of a multimodality management may improve the care of patients with locally advanced rectal cancer.
- After surgery for locally advanced rectal cancer, patients rate their HRQL lower compared to patients operated on for primary resectable rectal cancer and to the general Swedish population.

SAMMANFATTNING

Bakgrund

Cancer i tjocktarmen och ändtarmen är den tredje vanligaste cancerformen i Sverige, varav ändtarmscancer (rektalcancer) svarar för en tredje del av fallen. År 2003 diagnosticerades ca 1650 nya fall inom Stockholm-Gotland regionen. Ändtarmscancer drabbar ffa äldre och medianåldern vid diagnos är 70 år, cancerformen är vanligare hos män.

Definitionen av *lokalt avancerad primär rektalcancer* är att tumören har vuxit igenom tarmväggen och över på omgivande organ i lilla bäckenet. Mellan 10-15% av alla patienter som diagnostiseras med ändtarmscancer har en lokalt avancerad tumör. Återfall av tumören efter operation, sk lokalt recidiv har minskat kraftigt de senaste 20 åren och idag runt 5-15%. Minskningen av recidiven beror framför allt på att fler patienter får preoperativ strålbehandling och att den kirurgiska tekniken förbättrats genom införandet ny operationsmetod i början av 90-talet; Total Mesorectal Excision (TME) som innebär att tumören i ändtarmen opereras genom att ändtarmen med omgivande fettvävnad inkluderande lokala lymfkörtlar och kärl tas bort.

Behandling av patienter med lokalt avancerad ändtarmscancer och lokalt återfall är likartad, därför är båda dessa patientgrupper studerade gemensamt i avhandlingen.

Stockholm Colorectal Cancer Study Group bildades 1980 med syfte att förbättra omhändertagandet och behandlingen av patienter med tjock och ändtarmscancer. Ett flertal studier är genomförda och ett regionalt vårdprogram infört. Vid Onkologiskt Centrum har ett register av alla patienter med tjock- eller ändtarmscancer upprättats. Detta register innefattar information om patienterna, tumören och behandlingen med dess komplikationer och utfall, samt uppföljningsdata.

Utredning

Symptomen på ändtarmscancer är förekomst av blod och slem i avföringen samt ändrade avföringsvanor. Smärta är ett sent tecken, då är tumören ofta redan avancerad med överväxt på nerver eller också mycket lågt växande i ändtarmen.

Patienterna bör utredas genom undersökning av den lokala växten i lilla bäckenet med magnetkamera (MRI) eller ultraljud av ändtarmen samt vävnadsprov från tumören. Hela tjocktarmen bör undersökas med koloskopi för att finna eventuella samtida tumörer högre upp. För utredning av fjärrmetastaser görs undersökning av lungor och buk ffa lever, antingen med datortomografi (DT) eller ultraljud. Patienten bör därefter diskuteras på en multidisciplinär konferens (MDT) för att fastställa radiologiskt tumörstadium sk staging, samt lämplig preoperativ strål- och/eller cellgiftbehandling inför kirurgi.

Behandling

Ändtarmscancer är strålkänslig och ett flertal studier har visat lägre recidivfrekvens efter preoperativ strålning. Tillägg av cellgiftsbehandling vid lokalt avancerad ändtarmscancer samt vid återfall kan ge tumörminskning som underlättar den kirurgiska resektionen. Ofta får patienten strålning samt cellgifter under 5 veckor och därefter följer kirurgi ca 6-8 veckor senare för att stråleffekten på tumören ska ha lett till tumörsönderfall. Strålningen har dock en del biverkningar och skadar även frisk vävnad, vilket begränsar den maximala dos av strålning som kan ges.

Patienten opereras därefter med vid resektion av ändtarmen medtagande alla vävnader och organ i lilla bäckenet på vilka tumören växer över. Detta innebär ofta en mycket omfattande operation där urinblåsa, prostata hos män och gynekologiska organ hos kvinnan kan behövas tas bort. Ibland ges även intraoperativ strålbehandling (IORT) lokalt mot tumörområdet under operationen. Patienten får ofta en eller två stomier; för avföring och även ibland för urin.

Om tumören har spritt sig till lokala lymfkörtlar ges patienten ofta efterföljande cellgiftbehandling inom ramen för någon studie, då effekten av sk adjuvant cellgiftbehandling inte är säkerställd.

Överlevnad vid behandling av lokalt avancerad ändtarmscancer och återfall är helt beroende på operativ radikalitet.

Vid potentiellt radikal kirurgi är 5-års överlevnad 40-50%.

Det övergripande syftet med denna avhandling har varit att studera omhändertagande, resultat, prognos samt livskvalitet för patienter med lokalt avancerad ändtarmscancer eller återfall av ändtarmscancer.

Delarbete I

Patienter med lokalt avancerad primär ändtarmscancer bör utredas noggrant med hänsyn till tumörutbredning samt eventuell spridning. I detta arbete studerades hur den preoperativa utredningen påverkar preoperativ behandling, kirurgisk radikalitet, återfall och överlevnad. 303 patienter blev opererade för lokalt avancerad ändtarmscancer i Stockholm-Gotland regionen 1995-2004. Efter register- och journalgenomgång delades patienterna in i tre grupper efter graden av utredning och eventuell MDT diskussion.

Studien visade att radiologisk bedömning lokalt i lilla bäckenet och avseende fjärrmetastaser ökade antal patienter som fick preoperativ strålbehandling och cellgifter samt efterföljande radikala operationer. Detta ledde till en ökad överlevnad och bättre lokal tumörkontroll. Effekten av MDT konferenser var ökad andelen patienter som preoperativt behandlades samt fick radikal kirurgi, men någon förlängning av överlevnad kunde inte påvisas.

Delarbete II

Lokal recidiv av ändtarmscancer i Stockholm-Gotland regionen har minskat med införandet av strålbehandling och TME-kirurgi. Då ca 50% av de patienterna som får recidiv av sin ändtarmscancer får lokalt återfall utan fjärrmetastaser är det viktigt att upptäcka dessa tidigt och kirurgiskt behandla dem. Mellan 1995 och 2003 opererades 2318 patienter för primär rektalcancer. Efter uppföljning av dessa till jan 2005 hade 141 (6%) utvecklat ett lokalt recidiv. Behandling och prognos hos dessa patienter jämfördes med ett material från 1980-1991. Fyrtio procent av patienterna med lokalt återfall opererades, 34% fick palliativ strålbehandling och övriga endast symptomatisk behandling. Av de opererade blev knappt hälften radikalt opererade, 5-årsöverlevnaden hos dessa var 57% jämfört med en total 5-års överlevnad på 9%. I jämförelse med studien 1980-91 hade andelen som opererades samt andelen radikala operationer ökat och även 5-års överlevnad var högre; sannolikt resultat av förbättrat omhändertagande och utvecklad kirurgisk teknik.

Delarbete III

På Karolinska Universitetssjukhuset infördes 1991 ett multidisciplinärt program för omhändertagande av patienter med lokalt avancerad primär ändtarmscancer och lokalrecidiv. Delarbete III är en uppföljning dessa patienter fram till 2002. Av 58 patienterna med lokalt avancerad primär ändtarmscancer var 59% radikalt opererade. Dessa hade en 5-års överlevnad på 34%. Patienterna med lokala recidiv (64st) blev i 34% radikalt opererade med en 5-årsöverlevnad på 40%. Den postoperativa sjukligheten och komplikationsfrekvensen var hög och endast var femte patient var utan komplikationer.

Delarbete IV

Den extensiva kirurgin med dess komplikationer ger ökad överlevnad men också påverkan på livskvalitet. I delarbete IV har en livskvalitetsmätning utförts på de patienter som opererats för lokalt avancerad ändtarmscancer samt recidiv av ändtarmscancer på Karolinska Universitetssjukhuset 1991-2003 som levde år 2005. EORTCs validerade frågeformulär QLQ-C30 and QLQ-CR38 besvarades av 43/47 tumörfria patienter och jämfördes med en referensgrupp patienter som opererats för primärt operabel ändtarmscancer samt svensk normalbefolkning. Ett flertal funktioner undersöktes. Global livskvalitet, roll-, fysisk- och social funktion var lägre hos patienterna efter operation av avancerad ändtarmscancer. De uppgav även mer symptom av smärta och trötthet. Detta är viktigt att informera och förmedla till patienter och anhöriga inför kirurgi och för att kunna planera adekvat postoperativt support.

Sammanfattningsvis, kan patienter som drabbats av lokalt avancerad ändtarmscancer och lokalrecidiv botas, men det krävs ett multidisciplinärt omhändertagande med en omfattande och väl genomförd utredning följt av preoperativ cellgifts- samt strålbehandling och därefter extensiv radikal kirurgi och slutligen eventuell efterföljande cellgiftbehandling. Detta är en mycket krävande behandling för dessa patienter som påverkar deras livskvalitet. Behandlingens möjligheter till bot bör vägas mot komplikationrisken i varje enskilt fall i samband med MDT diskussioner.

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APPENDIX



EORTC QLQ-C30 (version 3)

Vi är intresserade av några saker som har med Dig och Din hälsa att göra. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på Dig. Det finns inga svar som är "rätt" eller "fel". Den information Du lämnar kommer att hållas strikt konfidentiell.

Var vänlig fyll i Dina initialer:

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När är Du född? (Dag, Månad, År):

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Dagens datum (Dag, Månad, År):

31

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		Inte alls	Lite	En hel del	Mycket
1.	Har Du svårt att göra ansträngande saker, som att bära en tung kasse eller väska?	1	2	3	4
2.	Har Du svårt att ta en <u>lång</u> promenad?	1	2	3	4
3.	Har Du svårt att ta en <u>kort</u> promenad utomhus?	1	2	3	4
4.	Måste Du sitta eller ligga på dagarna?	1	2	3	4
5.	Behöver Du hjälp med att äta, klä Dig, tvätta Dig eller gå på toaletten?	1	2	3	4

Under veckan som gått:

		Inte alls	Lite	En hel del	Mycket
6.	Har Du varit begränsad i Dina möjligheter att utföra antingen Ditt förvärvsarbete eller andra dagliga aktiviteter?	1	2	3	4
7.	Har Du varit begränsad i Dina möjligheter att utöva Dina hobbies eller andra fritidssysselsättningar?	1	2	3	4
8.	Har Du blivit andfädd?	1	2	3	4
9.	Har Du haft ont?	1	2	3	4
10.	Har Du behövt vila?	1	2	3	4
11.	Har Du haft svårt att sova?	1	2	3	4
12.	Har Du känt Dig svag?	1	2	3	4
13.	Har Du haft dålig aptit?	1	2	3	4
14.	Har Du känt Dig illamående?	1	2	3	4
15.	Har Du kräkts?	1	2	3	4
16.	Har Du varit förstoppad?	1	2	3	4

Fortsätt på nästa sida

Under veckan som gått:

	Inte alls	Lite	En hel del	Mycket
17. Har Du haft diarré?	1	2	3	4
18. Har Du varit trött?	1	2	3	4
19. Har Dina dagliga aktiviteter påverkats av smärta?	1	2	3	4
20. Har Du haft svårt att koncentrera Dig, t.ex. läsa tidningen eller se på TV?	1	2	3	4
21. Har Du känt Dig spänd?	1	2	3	4
22. Har Du oroat Dig?	1	2	3	4
23. Har Du känt Dig irriterad?	1	2	3	4
24. Har Du känt Dig nedstämd?	1	2	3	4
25. Har Du haft svårt att komma ihåg saker?	1	2	3	4
26. Har Ditt fysiska tillstånd eller den medicinska behandlingen stort Ditt <u>familjeliv</u> ?	1	2	3	4
27. Har Ditt fysiska tillstånd eller den medicinska behandlingen stort Dina <u>sociala</u> aktiviteter?	1	2	3	4
28. Har Ditt fysiska tillstånd eller den medicinska behandlingen gjort att Du fått ekonomiska svårigheter?	1	2	3	4

Sätt en ring runt den siffran mellan 1 och 7 som stämmer bäst in på Dig för följande frågor:

29. Hur skulle Du vilja beskriva Din hälsa totalt sett under den vecka som gått?

1 2 3 4 5 6 7

Mycket dålig

Utmärkt

30. Hur skulle Du vilja beskriva Din totala livskvalitet under den vecka som gått?

1 2 3 4 5 6 7

Mycket dålig

Utmärkt



EORTC QLQ – CR38

Patienter berättar ibland att de har följande symptom. Markera i vilken utsträckning som Du har haft dessa symptom under Den senaste veckan. Svara genom att ringa in Den siffra som bäst passar in på Dig.

Under veckan som gått:	Inte alls	Lite	En hel del	Mycket
31. Urinerade Du ofta under dagen?	1	2	3	4
32. Urinerade Du ofta under natten?	1	2	3	4
33. Har Du känt smärta eller sveda i samband med urinering?	1	2	3	4
34. Har Du känt Dig uppsvälld I magen?	1	2	3	4
35. Har Du haft buksmärter?	1	2	3	4
36. Hade Du ont i skinkorna?	1	2	3	4
37. Var Du besvärad av mycket gaser i magen?	1	2	3	4
38. Rapade Du?	1	2	3	4
39. Har Du gått ner i vikt?	1	2	3	4
40. Har Du varit torr i munnen?	1	2	3	4
41. Har ditt hår varit torrt och livlöst på grund av din sjukdom eller behandling?	1	2	3	4
42. Har mat och drycker smakat annorlunda än vanligt?	1	2	3	4
43. Har Du känt Dig mindre attraktiv på grund av sjukdomen eller behandlingen?	1	2	3	4
44. Har Du känt dig mindre kvinnlig/manlig på grund av din sjukdom eller behandling?	1	2	3	4
45. Har Du känt Dig missbelåten med din kropp?	1	2	3	4
46. Har Du varit orolig för din framtida hälsa?	1	2	3	4
Under de senaste <u>fyra</u> veckorna:	Inte alls	Lite	En hel del	Mycket
47. I vilken utsträckning har Du varit intresserad av sex?	1	2	3	4
48. I vilken utsträckning har Du varit sexuellt aktiv? (med eller utan samlag)	1	2	3	4
49. Besvara denna fråga endast om Du varit sexuellt aktiv: I vilken utsträckning har sex varit till glädje för Dig?	1	2	3	4

Fortsätt på nästa sida

Under de senaste fyra veckorna:

		Inte alls	Lite	En hel del	Mycket
Endast för män					
50.	Har Du haft svårt att få eller bibehålla en erektion?	1	2	3	4
51.	Hade Du problem med sädesuttömning (t.ex. så kallad torr sädesuttömning)?	1	2	3	4

		Inte alls	Lite	En hel del	Mycket
Endast för kvinnor som har haft samlag					
52.	Var Du torr i slidan under samlaget?	1	2	3	4
53.	Hade Du ont under samlaget?	1	2	3	4

54. Har Du stomi (kolostomipåse)? **Nej** Var god svara på frågorna 55 till 61
(Var god ringa in Nej eller Ja) **Ja** Var god hoppa över frågorna 55 till 61
och svara på frågorna 62 till 68

Under veckan som gått:

		Inte alls	Lite	En hel del	Mycket
Endast för patienter UTAN stomi (kolostomipåse)					
55.	Hade Du ofta behov att tömma tarmen under dagen?	1	2	3	4
56.	Hade Du ofta behov att tömma tarmen under natten?	1	2	3	4
57.	Har Du känt behov att tömma tarmen utan att i själva verket få avföring?	1	2	3	4
58.	Har Du haft någon ofrivillig tömning av tarmen?	1	2	3	4
59.	Har Du haft blod i avföringen?	1	2	3	4
60.	Har Du haft svårt att tömma tarmen?	1	2	3	4
61.	Har det varit smärtsamt att tömma tarmen?	1	2	3	4

		Inte alls	Lite	En hel del	Mycket
Endast för patienter MED stomi (kolostomipåse)					
62.	Var Du rädd att andra skulle kunna höra din stomi?	1	2	3	4
63.	Var Du rädd att andra skulle kunna känna lukten av din avföring?	1	2	3	4
64.	Var Du orolig för att stomipåsarna eventuellt skulle läcka?	1	2	3	4
65.	Har Du haft problem att sköta din stomi?	1	2	3	4
66.	Var huden runt stomin irriterad?	1	2	3	4
67.	Kände Du dig besvärad av din stomi?	1	2	3	4
68.	Kände Du dig mindre hel på grund av din stomi?	1	2	3	4

