SURGICAL TREATMENT OF COLORECTAL CANCER – CONTROVERSIAL ISSUES

by

Pirita Varpe

From the Department of Surgery, Turku University Hospital, Turku, Finland.

Supervised by

Docent Juha Grönroos, MD, PhD
Department of Surgery
University of Turku
Turku, Finland

and

Docent Arto Rantala, MD, PhD
Department of Surgery
University of Turku
Turku, Finland

Reviewed by

Docent Petri Aitola MD, PhD
Department of Gastroenterology and Alimentary Tract Surgery
Tampere University Hospital
Tampere, Finland

and

Pia Österlund MD, PhD
Department of Oncology
University of Helsinki
Helsinki, Finland

Dissertation opponent

Professor Jukka-Pekka Mecklin, MD, PhD
Department of Surgery
Central Finland Central Hospital
Jyväskylä, Finland

To Heli, Annika and Anssi

ABSTRACT

Pirita Varpe
Surgical treatment of colorectal cancer – controversial issues
From the Department of Surgery, University of Turku, Turku, Finland**.**
Annales Universitatis Turkuensis, Medica-Odontologica Series D, Turku, Finland, 2009.

Aims: This study was carried out to evaluate surgical treatment of colorectal cancer (CRC) with special interest in present status and controversial issues: stenting as a palliative procedure for metastasized CRC (I), duration of thromboprophylaxis after the surgical treatment of CRC (II), treatment of the increasing population of elderly people (III) and the quality of life (QoL) after surgery for rectal cancer with special reference to pelvic floor dysfunction (IV).

Materials and methods: The material consisted of patients with CRC operated on at Turku University Hospital between 2003 and 2008. In study II the data was collected retrospectively from electronic archives. In other studies the follow-up data was collected at postoperative control visits. In study IV the RAND-36 standardized questionnaire and additional questions assessing urinary, sexual and anorectal dysfunction were used.

Results: The results of the current study showed that self-expanding metallic stents provided an alternative to palliative surgery in the treatment of obstructive CRC. Low molecular heparin given s.c. for a median of 11 days until hospital discharge seemed to provide sufficient thromboprophylaxis after surgery. With preoperative selection elderly patients with rectal cancer were suitable for major surgery for rectal cancer with morbidity and mortality rates comparable to those in younger patients. There was no difference between preoperative and one year postoperative general QoL for operated rectal cancer patients. Postoperative pelvic dysfunction was associated with an impaired QoL in some dimensions.

Conclusions: Many individual factors regarding the patient and the disease must be taken into account when making treatment decisions in CRC to ensure successful treatment of CRC, patient satisfaction and QoL.

Key words: anorectal dysfunction, colorectal cancer, elderly, quality of life, self-expanding metallic stents, sexual dysfunction, thromboprophylaxis, urinary dysfunction.

TIIVISTELMÄ

Pirita Varpe
Suolistosyövän kirurginen hoito – kiistakysymyksiä
Kirurgia, Turun yliopisto, 20520 Turku
Annales Universitatis Turkuensis, Medica-Odontologica Series D, Turku, 2009.

Tausta: Tutkimuksen tarkoituksena oli arvioida suolistosyövän kirurgista hoitoa. Erityisesti huomioitiin kiistanalaiset näkökohdat kuten stentti-hoidon soveltuvuus levinneessä paksusuolisyövässä suolitukoksen hoitoon, laskimotukosten ehkäisyhoidon kesto paksusuolisyöpäleikkauksen jälkeen, ikääntyneiden potilaiden hoitokäytäntö ja lantion alueen ongelmat ja niiden vaikutus elämänlaatuun peräsuolisyöpäleikkauksen jälkeen.

Aineisto: Tutkimuksen aineisto koostui Turun yliopistollisessa keskussairaalassa vuosina 2003–2008 leikatuista suolistosyöpäpotilaista. Toisessa osatyössä potilastiedot kerättiin jälkikäteen potilaskertomuksista, muissa osatöissä potilaiden kontrollikäyntien yhteydessä. Neljännessä osatyössä elämänlaadun mittarina käytettiin RAND-36 tutkimuslomaketta sekä itselaadittuja lisäkysymyksiä koskien virtsaamis-, seksuaali- ja ulostamisvaikeuksia.

Tulokset: Tutkimuksen tulokset osoittivat, että stentti soveltuu hyvin levinneen suolistosyövän suolitukoksen hoitoon. Pienimolekylaarinen hepariini annettuna kerran päivässä keskimäärin 11 vuorokauden ajan sairaalassaoloaikana toteutettuna vaikuttaa olevan riittävä ennaltaehkäisy syviin laskimotukoksiin ja keuhkoveritulppaan. Nykytekniikalla tehtävä vaativampi radikaalikirurgia soveltuu myös ikääntyneille potilaille, tosin potilaan liitännäissairaudet ja yleiskunto tulee tarkasti arvioida ennen leikkausta. Peräsuolisyöpäleikattujen potilaiden elämänlaatu on vuosi leikkauksen jälkeen samanlainen kuin ennen toimenpidettä. Leikkauksen aiheuttamat ongelmat lantionalueella huonontavat joitakin elämänlaadun osa-alueita.

Johtopäätökset: Jokaisen suolistosyöpäpotilaan kohdalla tulee yksilöllisesti harkita syövän hoitovaihtoehdot, jotta varmistetaan tuloksellinen suolistosyövän hoito, potilaiden tyytyväisyys ja hyvä elämänlaatu hoidon jälkeen.

Avainsanat*: elämänlaatu, itselaajeneva metalliverkkostentti, laskimotukoksen ennaltaehkäisy, seksuaaliongelma, suolistosyöpä, ulostamisongelma, vanhuus, virtsaamisongelma.

TABLE OF CONTENTS

ABBREVIATIONS

ANOVA   analysis of variance
APR   abdominoperineal resection
AR   anterior resection
BP   body pain
CEA   carcinoembryonic antigen
CRC   colorectal cancer
CT   computed tomography
DCC   deleted in Colorectal Carcinoma
DVT   deep-vein thrombosis
ERUS   endorectal ultrasound
EV   energy and vitality
Gy   gray
HNPCC   hereditary non-polyposis colorectal cancer
HP   general health perception
LDUH   low-dose unfractionated heparin
LMWH   low-molecular-weight heparin
MF   mental functioning
MRI   magnetic resonance imaging
PE   pulmonary embolism
PF   physical functioning
QoL   quality of life
RAND-36   short-form health survey (SF-36)
RE   role limitations as a result of emotional problems
RP   role limitations as a result of physical problems
SAS   statistical analysis software
s.c.   subcutaneously
SEMS   self-expanding metallic stent
SF   social functioning
TME   total mesorectal excision
VTE   venous thromboembolism

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, which are referred to in the text by their Roman numerals (I-IV)

I   Varpe P, Huhtinen H, Rantala A, Salminen P, Sarparanta H, Grönroos J. Adoption of self-expanding metallic stents in the palliative treatment of obstructive colorectal cancer – look out for perforations!
Surg Laparosc Endosc Percutan Tech 2008; 18(4):353-6

II   Varpe P, Huhtinen H, Rantala A, Grönroos J. Thromboprophylaxis following surgery for colorectal cancer - is it worthwhile after hospital discharge?
Scand J Surg 2009; 98(1):58-61

III   Varpe P, Huhtinen H, Rantala A, Grönroos J. Age of the patient should not play a key role in clinical decision making on the surgical treatment of rectal cancer.
Aging Clin Exp Res, in press

IV   Varpe P, Huhtinen H, Rantala A, Salminen P, Rautava P, Hurme S, Grönroos J. Quality of life after surgery for rectal cancer with special reference to pelvic floor dysfunction.
Colorectal Dis, in press

The original publications have been reproduced with the permission of the copyright holders.

1.   INTRODUCTION

Colorectal cancer (CRC) is the third most common form of cancer worldwide with an estimated one million new patients diagnosed yearly (Parkin *et al.* 2005). Over thirty percent of patients with CRC are now over the age of 70 years in the Western world and in the future the elderly population and their life expectancy are estimated to rapidly increase (Abir *et al.* 2004; Finnish cancer registry 2007). A total of 2561 CRCs were diagnosed in Finland in 2007, of which 39% were rectal cancer (Finnish cancer registry 2007).

The surgical treatment of CRC has greatly improved during recent decades. Total mesorectal excision (TME) technique has established a worldwide position as the golden standard for the surgical treatment of rectal cancer. The introduction of this surgical technique has reduced local recurrences from the former rates of 20-40 % to 2-12 % (Enker 1997; Heald *et al.* 1982; Heald and Ryall 1986; Kapiteijn *et al.* 2001). The autonomic nerve preserving TME technique has also decreased, but not erased, urinary, sexual and anorectal dysfunction, which has improved the postoperative quality of life (QoL) of patients with rectal cancer. However, these patients still have worse social functioning than the normal population (Vironen *et al.* 2006).

Traditionally, in incurable metastatic CRC cases, colostomy, colorectal bowel resection or entero-enterostomy have been surgical alternatives in the palliation of colorectal obstruction (Joffe and Gordon 1981; Liu *et al.* 1997). Since the introduction of the self-expanding metallic stent (SEMS) in 1991, SEMS has provided an alternative to palliative surgery in preventing or relieving colorectal obstruction (Dohmoto 1991). Stenting has decreased the morbidity and mortality of CRC patients who need surgical palliation for bowel obstruction and has allowed a prompt start to the oncological treatment of these patients (Ptok et al. 2006). New oncological treatment strategies seem to increase the overall survival of metastasized CRC patients from 10 to 20-24 months (Hurwitz *et al.* 2004; Nordic Gastrointestinal Tumor Adjuvant Therapy Group 1992; Tournigand *et al.* 2006).

CRC surgery implies a high risk for postoperative thromboembolic complications (Geerts *et al.* 2008). Prophylaxis with low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin (LDUH) s.c. is recommended for CRC patients (Bergqvist 2004; Leonardi *et al.* 2007). The optimal duration of postoperative thromboprophylaxis after abdominal surgery for CRC has not yet been clearly defined (Bergqvist *et al.* 2002; Geerts *et al.* 2008).

In this thesis the feasibility, safety and efficacy of the surgical treatment of patients with CRC were analyzed. Studies were carried out with special interest in present status and controversial issues: stenting, thromboprophylaxis, aging and QoL.

2. REVIEW OF THE LITERATURE

2.1. Prevalence of colorectal cancer

CRC is the third most common form of cancer worldwide with an estimated one million new patients diagnosed yearly. As for deaths, CRC is the third most common cause of death from malignancy in males after pulmonary and prostatic cancer and in females the second most common after breast cancer (Parkin *et al.* 2005). In year 2007, a total of 2561 CRCs were diagnosed in Finland, of which 994 (39%) were rectal cancer. In Finland, the incidence of CRC is 27/100 000 among men and 19.5/100 000 among women (Finnish cancer registry 2007). In developed countries the prevalence of CRC is increasing all the time in the general population and particularly in elderly patients (Kiran *et al.* 2007).

2.2. Pathophysiology of colorectal cancer

The majority of CRCs are sporadic contributed to lifestyle and environmental factors, but a proportion (5-6%) has a clear genetic background often caused by a mutation in a single gene. There are two main clinical types of genetically determined predisposition to CRC: intestinal polyposis syndromes and hereditary non-polyposis CRC (HNPCC). The polyposis syndromes can be further divided into three different clinical entities: familial adenomatous polyposis, juvenile polyposis and Peutz–Jeghers polyposis (Arnold *et al.* 2005; Järvinen 2004). The hereditary forms of CRC are rare, but they are important to recognize because these patients have a cumulative lifetime CRC risk, increased risk for associated cancer and their families also need genetic counselling and screening colonoscopies (Mecklin 2008).

CRC mostly arises from adenomas recognized as colonic polyps, but may occasionally arise from sessile serrated adenoma (Cappell 2007; Mäkinen 2007). Adenomatous polyposis coli gene mutation is the key molecular step in adenoma formation. Progression from adenomas to colon cancer is a multistep process, involving mutations of the DCC, k-ras, and tumour suppression (p53) genes and loss of heterozygosis (Cappell 2007).

2.3. Diagnosis and preoperative staging

Many patients with CRC experience no symptoms in the early stages of the disease. When symptoms appear, they vary depending on the size and location of the tumour in the large intestine. The frequency of colorectal cancer in various parts of the colorectum is shown in Figure 1.
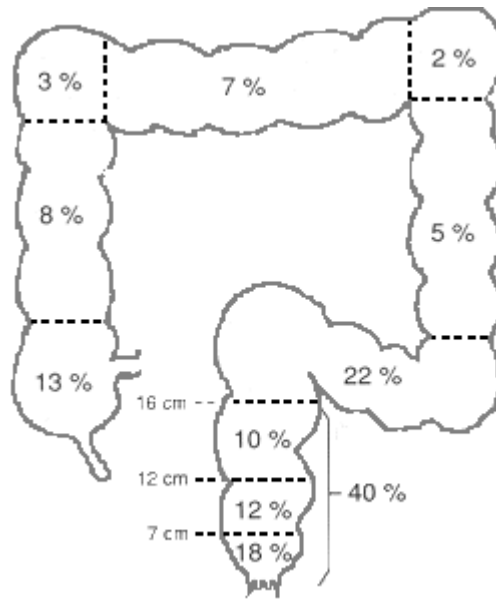
Figure 1. The frequency of colorectal cancer in various parts of the colorectum (Höckerstedt *et al.* 2000).

The symptoms of CRC depend on the location of the tumour. Common symptoms are changes in bowel functioning including diarrhea or constipation, changes in the appearance of stools such as melena or blood, anaemia, abdominal pain or unexplained weight loss.

It takes many years for CRC to develop from adenoma and early detection of CRC greatly improves the chances of cure. Therefore, screening for the disease is beneficial and recommended. Tests that have been considered for population screening include variants of the faecal occult blood test, flexible sigmoidoscopy and colonoscopy (Hewitson et al. 2007; Levin et al. 2008).

Carcinoembryonic antigen (CEA) level is recommended to be determined preoperatively. It is raised in 1/3 patients with CRC preoperatively. For the follow-up, CEA is most useful when found to be elevated preoperatively and then normalizes after resection of the tumour (Duffy *et al.* 2007; Renehan *et al.* 2002), but CEA also rises due to recurrent disease in at least 50% of patients with normal pre-operative values (Grossmann *et al.* 2007).

The diagnosis of CRC is usually made by colonoscopy, which enables the histological diagnosis. Virtual colonoscopy is a modern radiological method for investigating colon, but it lacks the possibility for histological diagnosis and

polyps found have to be removed by standard colonoscopy. For the same reasons the traditional double contrast barium is currently only rarely used (Rockey *et al.* 2005).

Tumour stage (Table1) at the time of the surgical treatment is the most important prognostic factor in CRC (Deans *et al.* 1992; Wiggers *et al.* 1988a). This staging also guides the decision of treatment of patients with CRC. The radiological preoperative staging of CRC is evaluated with whole body computed tomography (CT). The whole body CT is valuable in showing deep local invasion of the tumour and metastatic forms of the diseases, but it fails in early stage tumours and in pelvic disease (Akbari and Wong 2003; Van Cutsem *et al.* 2008)

The traditional clinical method for estimate of the local staging of rectal cancer is digital rectal exam. The mobility of the rectal tumour can be determined by digital rectal exam. The radiological possibility to evaluate the preoperative local status of rectal cancer is rectal magnetic resonance imaging (MRI) or endorectal ultrasound (ERUS). Rectal MRI and ERUS show better the depth of invasion of the rectal tumour and local lymph node involvement than CT. ERUS has been reported to be even better in showing the invasion of a rectal tumour and local lymph nodes than MRI, but MRI shows better other anatomy of the pelvis (Brown *et al.* 2004; Klessen *et al.* 2007). The quality of ERUS is also user dependent. In the future, three-dimensional ERUS may provide greater accuracy than conventional two-dimensional ERUS.

Limited studies exist on the use of positron emission tomography in primary tumour staging and it is not routinely used (Akbari and Wong 2003; Muthusamy and Chang 2007).

Table 1. Staging of colorectal cancer.

stage	TNM*	Modified Dukes`
I	T1-2 N0 M0	A
IIA	T3 N0 M0	B
IIB	T4 N0 M0	B
IIIA	T1-2 N1 M0	C
IIIB	T3-4 N1 M0	C
IIIC	any T N2 M0	C
IV	any T any N M1	D

*TNM classification presented here is according to the Staging of Colorectal Cancer: 2004 (Carolyn C. Compton and Frederick L. Greene)

T=primary tumour: TX=Primary tumour can not assessed, T0=No evidence of primary tumour, Tis=Carcinoma in situ:intraepithelial or invasion of lamina propria, T1=Tumour invades submucosa, T2=Tumour invades muscularis propria, T3=Tumour invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissues, T4=Tumour directly invades other organs or structures (T4a) and/or perforates visceral peritoneum (T4b).
N=Regional Lymph Nodes: NX=Regional lymph nodes can not be assessed, N0=No regional lymph node metastasis, N1=Metastasis in 1 to 3 regional lymph nodes, N2=Metastasis in 4 or more regional lymph nodes
M=Distant Metastasis: MX=Distant metastasis can not be assessed, M0=No distant metastasis, M1=Distant metastasis

2.4.   Surgical treatment

Surgical treatment is indicated in nearly all patients with newly diagnosed CRC unless survival is unlikely or life expectancy is very short due to advanced cancer or other diseases. Even in the presence of metastases, palliative surgical resection of the primary tumour may be advisable to prevent further bleeding and impending obstruction. Radical surgery is the main treatment of CRC and offers the only possibility of permanent cure.

2.4.1.   Open surgery

The standard approach to CRC is resection of the tumour-bearing segment of the bowel together with systematic removal of the draining lymphatics en bloc (Hohenberger *et al.* 2003; Huhtinen and Rantala 2006). Distal and proximal margins are recommended to be 5-10 cm (Nelson *et al.* 2001). The remaining parts of the colon are anastomosed together to create a functioning colon. When anastomosis is not possible, which sometimes happens with emergency

operations, a stoma is created (Bass *et al.* 2009). As for colonic cancers, depending on the location of the tumour the surgeon may select to do a right hemicolectomy, transverse colectomy, a left hemicolectomy or sigmoid resection. These operations are shown in Figure 2.
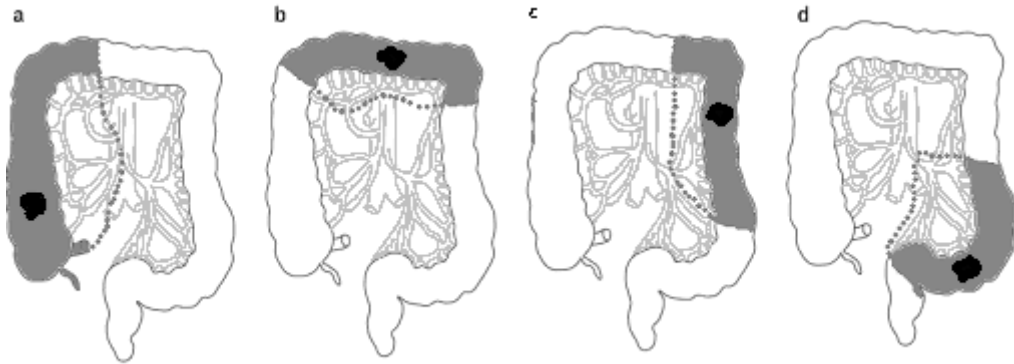
 Figure 2. The surgical treatment of CRC depending on the location of the tumour a) right hemicolectomy b) transverse colectomy c) left hemicolectomy d) sigmoid resection (the resection line is marked with dashed line).

Fifteen percent of CRCs occur when the tumour mass has become adherent to adjacent intra-abdominal organs or structures (Sugarbaker and Corlew 1982). The tumour is invasive in half of the cases due to the adhesions being inflammatory and the other half due to the size of the tumour. During surgery the difference between inflammatory adhesion and tumour invasion can not be recognized and therefore the primary tumour and adhered adjacent structures have been recommended to be removed en bloc. Touching the tumour during the operation should be avoided though studies on this are controversial (Turnbull *et al.* 1967; Wiggers *et al.* 1988b).

Rectal cancer surgery is more challenging than ordinary colon surgery due to the anatomy of rectum and pelvic floor. The surgical treatment of rectal cancer includes en bloc resection of the rectum as an intact unit with its lymphovascular drainage contained within the fascia propria of the mesorectum using sharp dissection techniques. On the other hand, the pelvic autonomic nervous system should be left intact for avoiding anorectal, urinary or sexual dysfunction. This technique is called total mesorectal excision (TME) (Heald *et al.* 1982) (Figure 3). The TME technique has established a worldwide position as the golden standard for the surgical treatment of rectal cancer (Enker 1997; Heald and Ryall 1986; Peeters *et al.* 2003).
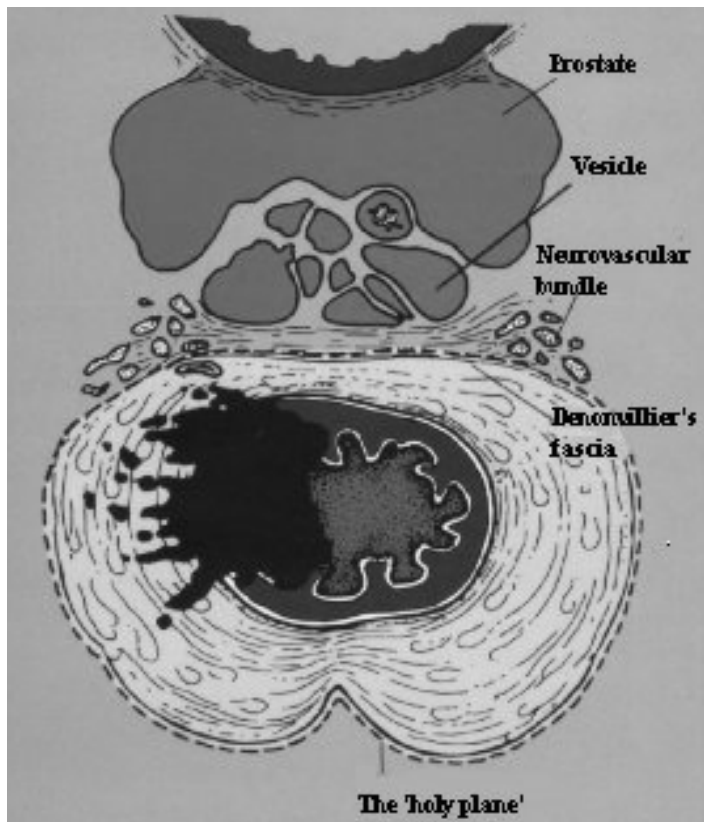
Reproduced with the permission of Bill Heald

Figure 3. Total mesorectal excision. The resection line is marked with a dashed line.

The standard operation for low- and midrectal tumours is anterior resection (AR) with TME. It has been shown that as long as the mesorectum is totally removed, a distal mucosal margin of at least 1 cm have to be reached (Karanjia *et al.* 1990; Kuvshinoff *et al.* 2001; Leo *et al.* 2008). In proximal rectal cancer, for which a 4–5 cm distal margin can be achieved, the transection of the rectum and mesorectum is performed above the pelvic floor. After high AR, the possibility for perfect recovery of anastomosis is better than after mid or low AR. After low AR colorectal or coloanal anastomosis can be performed using J-pouch, coloplasty or side-to-end anastomosis instead of end-to-end anastomosis (Brown *et al.* 2008; Lazorthes *et al.* 1986; Ulrich *et al.* 2005). Modern stapling instruments, the development of surgical techniques and preoperative oncological treatments enable low anastomoses and ensure that sphincter-sparing surgery can now be performed in 65-90 percent of patients with rectal cancer (Bujko *et al.* 2004; Meyerhardt *et al.* 2004; Ota *et al.* 2002). The technique of intersphincteric resection enables sphincter preservation even in

patients with carcinomas located at the anorectal junction, if not infiltrating to the anal sphincter (Fucini *et al.* 2002; Rullier *et al.* 2005; Rullier *et al.* 2003). Abdominoperineal resection (APR) is still often needed when an adequate distal resection marginal can not be reached and in advanced tumours. The perineal phase of APR is the difficult part of operation, often done synchronously with the abdominal phase and with the patient in the supine position. The rate of perineal wound complications after APR with primary perineal closure varies between 35-63 % (Bullard *et al.* 2005; Petrelli *et al.* 1986).With conventional techniques the risk of inadvertent perforation is high, the resulting specimen frequently has a waist at the lower border of the mesorectum and the circumferential resection margin is often close to the rectal muscle tube. (Nagtegaal *et al.* 2005). This generally leads to significantly higher local relapse rates 22.3% after APR when compared with AR 13.5% (Marr *et al.* 2005). As an alternative to conventional APR, the posterior perineal approach with gluteus maximus flap reconstruction of the pelvic floor has been used. This technique has a low risk of bowel perforation, the circumferential resection margin involvement and local perineal wound complications (Holm *et al.* 2007).

2.4.2. Laparoscopic surgery

Laparoscopic surgical techniques are widely used as a standard procedure for surgery for colon cancer and at some institutions for rectal cancer. Several clinical trials have shown that in the short-time outcome laparoscopic approach for CRC is associated with a shorter hospital stay, less postoperative pain, shorter duration of postoperative ileus, decreased morbidity and improvements in the quality of life (QoL). In the long-term, there has been no difference in morbidity, the rates of recurrence or cancer-related mortality between laparoscopic and open surgery (Fleshman *et al.* 2007; Guillou *et al.* 2005; Lacy *et al.* 2002; Leung *et al.* 2004; Veldkamp *et al.* 2005). The technique of laparoscopic colorectal surgery is demanding but in experienced hands, laparoscopic colorectal resection can be performed safely for all, also for ''high-risk" surgical patients and the elderly (Chautard *et al.* 2008; Marks *et al.* 2008).

2.4.3. Local surgery

In general, local treatment of CRC, including endoscopic removal of colonic polyps and transanal resection of the rectal tumour, has become widely accepted. Transanal local excision is useful with curative intent for T1, well-differentiated rectal cancers that are under 3 cm in diameter and occupy under 40 % of the circumference of the rectal wall (Sengupta and Tjandra 2001). The depth of mural penetration is correlated with the risk of nodal metastases. For

T1 tumours the risk of associated nodal metastases is 6-11% and for T2 tumours 10-20% (Tjandra *et al.* 2005). Local excision should be reserved for low-risk cancers in patients who accept an increased risk of tumour recurrence, prolonged surveillance, and possible need for aggressive radical surgery in the follow-up (Bentrem *et al.* 2005) or for patients with very poor general condition as a palliative procedure.

One possibility for local surgery is transanal endoscopic microsurgery (Baatrup *et al.* 2009; Buess *et al.* 1988b; Dias *et al.* 2009) , which combines the exposure of endoscopy with advanced instrument technology. This technique (Buess *et al.* 1988a) enables better access to lesions in the middle and upper rectum, but it is demanding because the dissecting instruments are inserted in parallel lines and visual imaging is achieved through a binocular stereoscope. The considerable skill required for performing these procedures and the perceived high capital cost of the system means it has become the domain of only a few surgeons (Saclarides 1997).

2.4.4.   Surgical palliation

Almost one fourth of the patients have metastases at the time of diagnosis of CRC (Ballantyne and Quin 1993). Unfortunately, only a small proportion of the patients with metastatic disease are candidates for curative surgery (Ballantyne and Quin 1993; Millikan *et al.* 1997). For the remaining majority, the therapeutic aim is to provide optimal palliation in terms of survival and QoL. Surgical palliation is needed if tumour dissemination or local spread causes obstruction and/or bleeding.

Traditionally, in incurable CRC cases, colostomy, colorectal bowel resection or entero-enterostomy have been the surgical alternatives in the palliation of colorectal obstruction. However, the former operations do not improve survival, but increase morbidity (Joffe and Gordon 1981; Liu *et al.* 1997). In addition, traditional surgical palliation of obstruction hampers the prompt start of oncological treatment.

Bowel obstruction is the first symptom in 7-29 % of CRC patients (Deans *et al.* 1994). Acute malignant colorectal obstruction is thus a frequently encountered surgical emergency. Emergency operations involving the unprepared and obstructed bowel result in increased mortality and high postoperative morbidity rates and poorer cancer-specific survival (Bass *et al.* 2009; Kyllönen 1987; McArdle *et al.* 2006).

Since its introduction in 1991, self expanding metallic stents (SEMS) have provided an alternative to palliative surgery in preventing or relieving colorectal

obstruction (Dohmoto 1991). Over the last decade, the use of SEMS has markedly increased and it seems to be an effective alternative in the palliative treatment of patients with malignant colorectal obstruction particularly in the left-sided colon (Alcantara *et al.* 2007; Repici *et al.* 2007; Repici *et al.* 2000; Sebastian *et al.* 2004). SEMS has also been effective as a bridge to surgery to enable a single - stage surgical procedure and avoid temporary or permanent stoma (Alcantara *et al.* 2007; Fregonese *et al.* 2008; Stipa *et al.* 2008). This temporary procedure gives the opportunity to perform accurate tumour staging, leading to avoidance of surgery in patients with disseminated disease or unacceptable surgical risk.

The technical success rate of SEMS application in palliative indication ranges between 64 % and 100 % and the clinical success rate between 55 % and 100 % (Alcantara *et al.* 2007; Repici *et al.* 2007; Repici *et al.* 2000; Sebastian *et al.* 2004).

The complication rate related to stent application ranges from 25 % to 40 %, with most complications being minor (Law *et al.* 2004; Suzuki *et al.* 2004). Perforation of the bowel is the most dangerous complication of stenting. Perforations related to the stent placement have been reported on an average in 4 % of the cases (Crosta *et al.* 2006; Sebastian *et al.* 2004). The perforations are related to the guidewires, balloon dilatation and expansion of the stent phases at the stenting procedure (Camunez *et al.* 2000; Sebastian *et al.* 2004). A randomized trial comparing surgery with stenting for incurable left-sided malignant colonic obstruction had to be stopped because of an unexpectedly high number of perforations; also late perforations in the stented group occurred (van Hooft *et al.* 2008). Other complications such as migration of the successfully inserted SEMS (12 %) and reobstruction after stenting (7 %) have also been reported (Sebastian *et al.* 2004). Minor complications such as rectal bleeding (5%), transient anorectal pain (5%) and fecal impaction can mostly be managed conservatively.

2.5. Adjuvant treatment

2.5.1. Preoperative radiotherapy

In an attempt to improve local control and survival after surgery alone (rate of local recurrences 30-40% and cancer specific survival 50-70% depending on stage of the tumour) post- and preoperative radiotherapy have been studied. The Colorectal Cancer Collaborative Group meta-analysis of trials comparing surgery and postoperative radiation vs. surgery alone showed that postoperative radiotherapy significantly reduced local recurrence, but overall survival was unaffected (Colorectal Cancer Collaborative Group 2001). In the Swedish randomized trial (Folkesson *et al.* 2005; Frykholm *et al.* 1993) that compared

preoperative and postoperative radiotherapy, the superiority of preoperative radiotherapy for local control and improved survival rate was shown. In the Swedish study, the surgical technique was conventional. A later created Dutch-Swedish trial (Kapiteijn *et al.* 2001) to evaluate the role of preoperative radiation with TME, showed the effect of preoperative short-term radiotherapy on local control (rate of local recurrences 2.4 vs 8.2%) in patients with clinically resectable rectal cancer, but there was no effect on overall survival. Later studies have verified the benefit of preoperative radiotherapy for reducing local recurrence rates, but the influence on survival is still controversial (Folkesson *et al.* 2005; Kapiteijn *et al.* 2001; Latkauskas *et al.* 2009; Peeters *et al.* 2007; Penopoulos *et al.* 2008). The addition of chemotherapy to long-term preoperative radiation was shown to further increase tumour downstaging and enhance sphincter preservation, but there was no difference in resectability or minor complications (Bosset *et al.* 2005; Gerard *et al.* 2006; Valero *et al.* 2003). However, the risk for leakage of low anastomosis is increased (Jestin *et al.* 2008). Preoperative radiation therapy also doubles the rate of total and major perineal wound complications after APR (Bullard *et al.* 2005; Chadwick *et al.* 2006). Preoperative chemoradiotherapy is more beneficial and has less toxicity for patients with resectable rectal cancer than postoperative chemoradiotherapy (Sauer *et al.* 2004).

Preoperative short-course radiotherapy 25 Gy in 5 Gy fractions during one week is given for T3 mid and low rectal cancers and the tumour is operated within one week. Neoadjuvant long course radiotherapy 50-54 Gy in 1.8-2 Gy fractions during five to six weeks is used for large fixed tumours for downstaging and -sizing. The patient is operated after 5 to 8 weeks after finishing long course radiotherapy (Frykholm *et al.* 1993; Kapiteijn *et al.* 2001).

In long term follow-up small bowel obstruction is more common in rectal cancer patients treated with preoperative radiation therapy than in those treated with surgery alone (Birgisson *et al.* 2008).

2.5.2. Postoperative adjuvant treatment

The role of adjuvant chemotherapy in radically treated CRC patients has been established in a large number of clinical trials. For patients with Stage III colon cancer, an overall survival benefit for fluorouracil-based chemotherapy has been firmly established, and recent data have shown further efficacy through the inclusion of oxaliplatin in adjuvant treatment programs (Andre *et al.* 2004; Haller *et al.* 2009; Krook *et al.* 1991; Moertel *et al.* 1990; Moertel *et al.* 1995).

For patients with Stage II colon cancer, the use of adjuvant chemotherapy remains controversial, but may be appropriate in individuals at moderate to high risk for disease recurrence (Benson *et al.* 2004; Wolpin *et al.* 2007). These high risk factors are inadequate lymph node sampling, poorly differentiated histology, lymphovascular or perineural invasion, T4 tumorstage, clinical bowel obstruction or perforation and an elevated preoperative plasma level of CEA (Van Cutsem *et al.* 2002). A combination of biological agents, such as cetuximab and bevacizumab, in treatment of metastatic disease optimize the oncological treatment of patients with metastasized CRC (Hurwitz *et al.* 2004; Ristamäki *et al.* 2006) and are studied in the adjuvant setting with the first report being negative (Wolmark *et al.* 2009).

Adjuvant treatment initiation later than three months after surgery for colorectal cancer has been shown not to be useful for colorectal cancer patients (Hershman *et al.* 2006), but there are also controversial studies (Arkenau *et al.* 2003; Chau *et al.* 2005). The adjuvant treatment should ideally be started within six weeks after surgery.

Patients with metastatic CRC cancer represent a very heterogeneous population and it is difficult to define a unique oncologic treatment for them, but modern chemotherapy with or without biologics has been shown to be useful. The overall survival of these patients seems to have increased from 10 to 20-24 months (Hurwitz *et al.* 2004; Nordic Gastrointestinal Tumor Adjuvant Therapy Group 1992; Tournigand *et al.* 2006).

2.6.   Complications connected to surgery

2.6.1.   Morbidity and mortality

Postoperative morbidity after the CRC operation has ranged from 12% to 40% and mortality from 0% to 12%. Significant influencing factors are the presence and number of concomitant diseases, the surgical procedure, the institution and the timing of operation such as elective or emergency procedure (Ascanelli *et al.* 2003; Hohenberger *et al.* 2003; Law and Chu 2004).

The most dangerous surgical complication is anastomotic leak. The incidence of an anastomotic leakage is lower in colon cancer surgery (3%) than in rectal cancer surgery (20%) (Hohenberger *et al.* 2003; Nesbakken *et al.* 2002). With low rectal anastomosis, diverting stoma is recommended to be used for fewer consequences if leakage occurs (Bax and McNevin 2007; Jestin *et al.* 2008; Tan *et al.* 2009). The other complications connected to surgery of CRC are wound healing disorders such as abdominal wall abscesses, haematomas, seromas and suture dehiscence, intra-abdominal abscesses, ileus and adhesions resulting in

bowel occlusions. The most important nonsurgical complications are cardiopulmonary disturbances and renal complications (Hohenberger *et al.* 2003).

2.6.2.   Thromboembolic complication

Venous thromboembolism (VTE) manifesting as a deep-vein thrombosis (DVT) or pulmonary embolism (PE) is a common complication of cancer (Lee and Levine 2003). Cancer patients undergoing surgery have at least a doubled risk of postoperative DVT and more than a triple risk of fatal PE compared to noncancer patients undergoing the same operations (Alizadeh and Hyman 2005; Borly *et al.* 2005; Geerts *et al.* 2008). The incidence of DVT in patients who undergo colorectal surgery and who do not receive thromboembolic prophylaxis is approximately 30% and the risk of fatal PE is 1% (Gukovsky-Reicher *et al.* 2003). The high risk of thrombotic complication is associated with pelvic dissection, the position of the patient (use of stirrups) during surgery and the presence of additional risk factors common to this patient group, such as cancer, advanced age and heart or respiratory failure, all known to introduce a hypercoagulable state (Alizadeh and Hyman 2005; Bergqvist 2006).

The conventional methods for preventing DVT are early mobilization and graded compression stockings. Intermittent pneumatic compression devices and venous foot pump also increase venous outflow and protect patients from VTE (Geerts *et al.* 2008; Glimelius *et al.* 2003; Suzuki *et al.* 2004).

There is strong evidence that low-dose unfractionated heparin (LDUH) and low-molecular-weight heparin (LMWH) are safe and effectively reduce the risk of DVT and fatal PE (Bergqvist 2004; Bergqvist *et al.* 2002; Borly *et al.* 2005; Geerts *et al.* 2008; Leonardi *et al.* 2007). Therefore, routine thromboprophylaxis is strongly recommended for patients undergoing colorectal surgery (Geerts *et al.* 2008). Although laparoscopic technique diminish surgical trauma, it may increase the risk of thrombosis by increasing abdominal pressure (Holzheimer 2004). Earlier clinical trials (Bergqvist *et al.* 2002; Rasmussen *et al.* 2003) have shown that LMWH prophylaxis for three weeks after hospital discharge substantially reduces the risk of late nonsymptomatic DVT. On the other hand, the majority of DVTs occur within two weeks after surgery, while VTE complications including PE may also occur later (Glimelius *et al.* 2003). The optimal duration of postoperative thromboprophylaxis after abdominal surgery for CRC has not yet been clearly defined (Bergqvist *et al.* 2002; Geerts *et al.* 2008; Glimelius *et al.* 2003). According to the latest recommendation for patients undergoing major general surgical procedures thromboprophylaxis should be continued until discharge

from hospital. For selected high-risk patients, including some of those who have undergone a major cancer operation or have previously experienced VTE, thromboprophylaxis with LMWH should be considered after hospital discharge for up to 28 days (Geerts *et al.* 2008).

2.6.3. Anorectal dysfunction after rectal cancer

The worsening of QoL after AR is associated with anorectal dysfunction, which has been shown to occur in 30-70 % of patients after AR (Camilleri-Brennan and Steele 1998; Vironen *et al.* 2006). Defecation symptoms such as increased bowel function, irregular bowel movements, urgency, obstructed defecation and impairment of continence manifest after AR (Ortiz and Armendariz 1996; Rasmussen *et al.* 2003). Impairment of continence after AR seems to be multifactorial, including diminished rectal capacity and dysfunctional adaptation, lowered internal anal sphincter tone, and loss of rectoanal inhibitory reflex (Batignani *et al.* 1991; Lee and Park 1998). These dysfunctions are mainly the result of damage to the autonomic pelvic nerves (Figure 4) during rectal mobilization at surgery (Tomita and Igarashi 2008). The distance of anastomosis from the anal verge has an influence on anorectal dysfunction. Patients with lower resection or anastomosis have a higher incidence of anorectal dysfunction (Havenga *et al.* 1996; Rasmussen *et al.* 2003). Part of the anorectal dysfunction results from the surgical techniques used in low anastomosis. The functional outcome can be improved by using a colonic J-pouch, coloplasty or side to end anastomosis (Brown *et al.* 2008; Fazio *et al.* 2007; Machado *et al.* 2003; Willis *et al.* 2001). Anastomotic leakage may impair long-term functional outcome (Hallbook and Sjodahl 1996), but controversial results have also been published (Bittorf *et al.* 2003). A certain number of symptoms present with unsatisfactory anorectal function after the operation seem to subside or diminish over time (Engel *et al.* 2003; Keighley and Matheson 1980). Preoperative short course radiotherapy has been shown to further impair anorectal function (Lundby *et al.* 2005; Murata *et al.* 2008; Nagtegaal *et al.* 2005; Pollack *et al.* 2006). However, there are also controversial reports in the literature regarding this issue (Pietrzak *et al.* 2007; Pietsch *et al.* 2007). The intersphincteric resection of the rectum leads to impaired postoperative continence and has been shown to cause daytime anal incontinence in 15-54 % and nocturnal incontinence in 20-76% of the patients (Bittorf *et al.* 2004; Tilney and Tekkis 2008) and the QoL is worse than compared with conventional coloanal anastomoses (Bretagnol *et al.* 2004).

### 2.6.4. Sexual and urinary dysfunction after rectal cancer

Surgical damage to the pelvic autonomic nerves is believed to be an important cause of urinary dysfunction as well as sexual dysfunction. The nerve complexes that are involved in normal genitourinary function and which can be

damaged during the surgical dissection are shown in Figure 4. Damage to the superior hypogastric plexus causes reduced bladder capacity and may result in urge incontinence and difficulty with ejaculation. Damage of inferior hypogastric plexus may lead to overflow incontinence, urinary retention, difficulty in bladder emptying and erectile dysfunction (Kellokumpu and Mecklin 2002; Lange *et al.* 2008).

After the introduction of the nerve preserving TME technique for rectal cancer surgery the incidence of urogenital dysfunction has decreased slightly. The incidence varies between 0-40% for bladder dysfunction and 10-70% for sexual dysfunction (Bohm *et al.* 2008; Moriya 2006; Nesbakken *et al.* 2000). The most common symptoms of urinary dysfunction are stress incontinence, urgency, elevated frequency of voiding, difficulty in emptying the bladder, loss of sensation of fullness of the bladder and overflow incontinence. Postoperative bladder dysfunction is associated with a high degree of reversibility (Del Rio *et al.* 2004). With modern operation technique permanent major urinary dysfunction is rare, but minor urinary dysfunction causes difficulties in social functioning (Maas *et al.* 2000; Vironen *et al.* 2006).

After the surgical treatment of rectal cancer sexual dysfunction is often due to multiple physiological and psychological causes (Hendren *et al.* 2005) and many patients also have pre-existing sexual dysfunction. In male patients physiological sexual dysfunction manifests as erectile dysfunction and retrograde ejaculation (Moriya 2006). These problems were most severe within patients operated with APR (Schmidt *et al.* 2005b). Erectile dysfunction often seems to be permanent, since it did not improve within six months after surgery (Maas *et al.* 2000). In women, information on sexual function is not easily obtained, but women seem to have some problems, but less functional problems than men after surgery for rectal cancer (Bohm *et al.* 2008). It seems that radiotherapy increases sexual dysfunction, but there is no difference between patients receiving short-course radiotherapy and those receiving long chemoradiation (Nagtegaal *et al.* 2005; Pietrzak *et al.* 2007). Sexual dysfunction is a multifactorial problem and it should be discussed with rectal cancer patients and efforts to prevent and treat it should be increased (Hendren *et al.* 2005; Vironen *et al.* 2006).

Open rectal cancer resection is associated with a higher rate of sexual dysfunction, but not bladder dysfunction, compared with laparoscopic surgery. The proposed advantages can be attributed to improvement in visibility by the magnification feature of laparoscopic surgery (Asoglu *et al.* 2008), but there have also been studies indicating the opposite (Jayne *et al.* 2005).
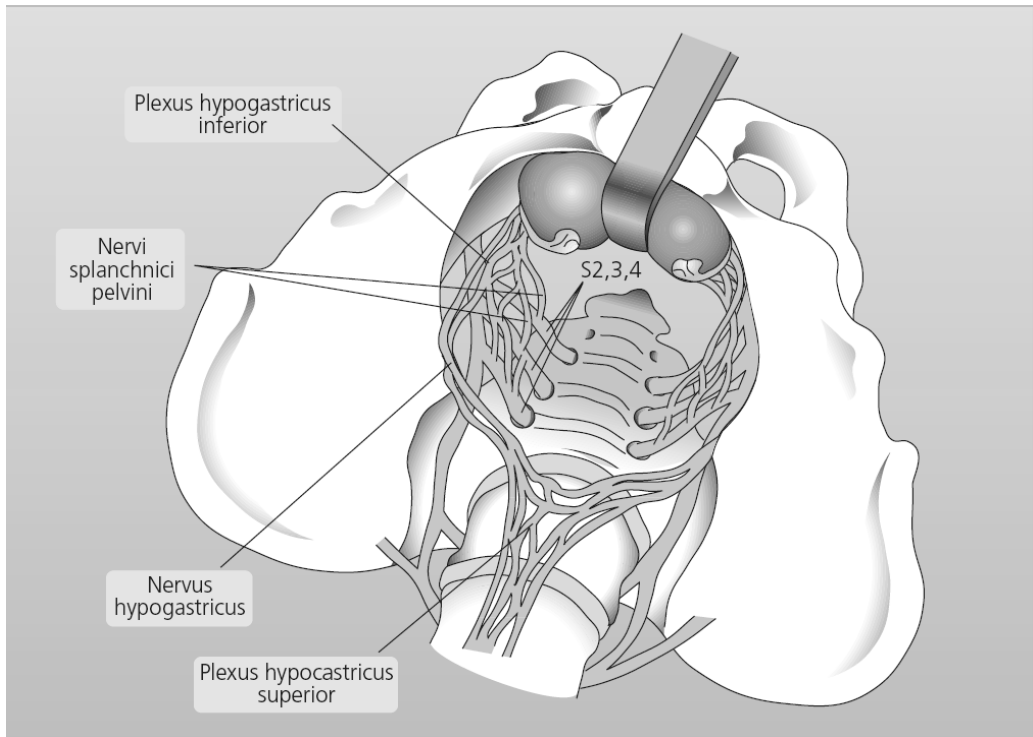
Reproduced with the permission of the copyright holder (Duodecim)

Figure 4. The pelvic autonomic nerve system. The sympatic nerve bundles stem from the level of Th12-L3 and create the superior hypogastric plexus, which divides into two hypogastric nerves at the sides of the pelvis. The parasympatic nerve bundles stem from the level of S2-S4. Sacral splanchnic nerves and hypogastric nerves create the inferior hypogastric plexus.

2.7. Prognosis

Tumour stage (Table1) at the time of surgery (Deans *et al.* 1992; Wiggers *et al.* 1988a) and adequate lymph node evaluation are key for prognosis (Chang *et al.* 2007; Edler *et al.* 2007; Swanson *et al.* 2003). Three factors have an effect on lymph node evaluation: patient derived impaired immunological reaction, surgeon related small resection or pathologist has not found enough lymph nodes although they were resected. Logoregional recurrences after surgical treatment of colonic cancer are less common than after surgery for rectal cancer (Hohenberger *et al.* 2003; Yun *et al.* 2008). By using TME technique, local recurrences have been reduced from the former rates of 20-40 % to 2-12 % (Enker 1997; Heald *et al.* 1982; Heald and Ryall 1986; Kapiteijn *et al.* 2001). Detailed pathologic examination, including the status of circumferential marginal is advocated since it provides accurate prognostic information (Wang

et al. 2009). The position and distance of the tumour within the circumference of the rectum is important for the prognosis. An anterior rectal tumour tends to be more advanced and, at least in male patients, has a higher risk of recurrence and death than tumours in other locations in the rectum (Lee *et al.* 2005). The probability of distant metastases depends on the disease stage and the presence of distant metastases has a major impact on the survival of patients with CRC. The 5-year survival of CRC is shown in Table 2.

Table 2. 5-year survival of patients with colorectal cancer (Macdonald 1999).

TNM classification	5-year survival %
T1-2N0M0	85-95
T3-4N0M0	60-80
T1-4N1-2M0	30-60
T1-4N0-2M1	<5

2.8.   Elderly patients - special considerations

In the developed countries the proportion of elderly people is increasing all the time. Age, taken as an independent predictor of outcome has no effect on the long-term survival of patients with CRC (Abir *et al.* 2004; Endreseth *et al.* 2006; Vironen *et al.* 2004). Instead, elderly patients have more comorbidities and the quality of their remaining life has to be kept in mind when deciding on surgical procedures and adjuvant treatments for fragile patients (Abir *et al.* 2004; Endreseth *et al.* 2006; Le *et al.* 2007; Vironen *et al.* 2004). However, despite more concomitant diseases that elderly patients may have, the cancer-specific-survival after surgery seems to be similar to that of younger patients (Endreseth *et al.* 2006; Law *et al.* 2006; Meyerhardt *et al.* 2004; Vironen *et al.* 2004). There are some reports available that recent advances in surgical techniques including TME, laparoscopic techniques, endoscopic palliation with SEMS and adjuvant treatments have decreased morbidity and mortality in elderly patients with rectal cancer but additional studies have been warranted (Feng *et al.* 2006; Hotta *et al.* 2007; Law *et al.* 2006; Puig-La Calle *et al.* 2000). The wide variety of treatment strategies for rectal cancer makes individual treatment plans possible. Thorough preoperative risk assessment, careful selection of patients for major surgery, a standardized surgical technique and

improved perioperative care are essential in keeping morbidity and mortality rates acceptable in elderly CRC patients (Vironen *et al.* 2004).

2.9. Quality of life after surgery for rectal cancer

Earlier studies (Rauch *et al.* 2004; Vironen *et al.* 2006) have shown that QoL after rectal cancer surgery can be the same or even better than that of the general population, but the results have been controversial. The effect of geographic factors such as weather, religion, or culture, should be taken into account when QoL evaluations are considered (Holzer *et al.* 2005; Kuzu *et al.* 2002). Some dimensions of QoL have been shown to decrease among patients who have undergone rectal cancer surgery. Pelvic dysfunction seems to be a major course of impaired QoL in some dimensions of QoL. Anorectal and urinary dysfunction have been shown to be the main reasons for weakened social functioning (Rauch *et al.* 2004; Vironen *et al.* 2006) and permanent stoma the reason for weakened physical functioning (Engel *et al.* 2003; Jess *et al.* 2002), but recent studies found equal or even better QoL in patients after APR compared with those who underwent AR (Schmidt *et al.* 2005a; Vironen *et al.* 2006). One explanation of the good postoperative general QoL after a rectal cancer operation may be preoperative symptoms and distress in addition to the "response shift" phenomenon at one year after the operation. The "response shift" means that patients who have survived a life-threatening disease, seem to develop a conscious awareness leading to positive appreciation of everyday life (Davies *et al.* 2009; Rauch *et al.* 2004). The QoL after rectal cancer surgery changes with time. It is generally the worst in the early postoperative period (Camilleri-Brennan and Steele 2001), but seems to improve within time, especially after low AR (Engel *et al.* 2003).

The postoperative QoL after a laparoscopic operation for rectal cancer seems to be better than after an open operation (Yang *et al.* 2007). Patients treated with short-course preoperative radiotherapy had worse continence-related QoL than patients treated with surgery alone for rectal cancer (Murata *et al.* 2008). QoL and anorectal and sexual functioning did not differ in patients receiving short-course radiotherapy, as compared to those receiving chemoradiation (Pietrzak et al. 2007).

3.   AIMS OF THE STUDY

The aim of the present study was to investigate the surgical treatment of colorectal cancer with special interest in present status and controversial issues, which were as follows:

1)   The safety and efficacy of SEMS in the palliative treatment of obstructive colorectal cancer

2)   The occurrence of symptomatic VTE after surgery for colorectal cancer in patients in whom LMWH was continued only until hospital discharge

3)   The effects of aging on the choice, feasibility and safety of different treatment modalities in patients with rectal cancer

4)   The QoL and occurrence of pelvic dysfunction after surgical treatment for rectal cancer

4. PATIENTS AND METHODS

4.1. Patients and follow-up

4.1.1. Patients who underwent stenting procedure (I)

During 2003-2006, a total of 26 patients (9 females and 17 males; mean age 69 years, range 39-85) underwent the stenting procedure at Turku University Hospital due to incurable obstructive CRC.

Twenty-two of these patients had multiple metastases, which were detected by CT. The remaining four patients were not suitable for radical therapy because of poor general condition. All patients presented with clinical symptoms and signs of bowel obstruction. The cancer diagnosis was confirmed in all cases by a histopathological examination. The tumour was located in the rectum in eight patients, in the sigmoid colon in seventeen patients and in the ascending colon in one patient (Table 6).

The follow-up data was collected at postoperative control visits. The mean follow-up time for all patients was 178 days (range 3-675). Three patients died within one week of SEMS insertion due to perforation. During the follow-up, 11 patients died of progression of CRC after a median survival period of 66 days. The remaining 12 patients were still alive on an average of 292 days (range 114-675) after the primary procedure.

4.1.2. Patients with CRC - special interest in thromboprophylaxis (II)

During 2003-2006, a total of 494 patients (254 females, 240 males; mean age 69 years, range 27-95) underwent abdominal surgery (only first procedure included) for CRC at Turku University Hospital. 110 of these patients had metastatic CRC and 173 had rectal cancer. The surgical procedures performed are shown in Table 3.

Table 3. Surgical procedures on CRC patients (Study II).

surgical procedure	number of patients
ileocecal resection	5
right hemicolectomy	111
resection of transverse colon	7
left hemicolectomy	19
sigmoid resection	
other resection of colon	12
Hartman procedure	15
anterior resection	125
abdominoperineal resection	58
subtotal colectomy	8
reversal of Hartman procedure	2
laparotomy and sigmoidostomy	2
ileotransversostomy	10
gastrojejunostomy	4
resection of small intestine	3
explorative laparotomy	35

Reproduced with the permission of the copyright holder

For thromboprophylaxis enoxaparin (Klexane®; 40mg s.c.) was started in all patients 12 hours before surgery and continued at a once-daily dose until hospital discharge. Median length of prophylaxis was 11 days (range 1-55). All patients wore graded knee length compression stockings (TED®) from the operation day to full mobilisation (average 2 days) and were mobilised on the operation day or the first postoperative day.

The follow-up data for the 494 patients was collected from the electronic archives covering all hospitals situated within the Hospital District of Southwest Finland and analyzed for up to three months after the operation with special reference to the occurrence of clinical and symptomatic VTE. The follow-up time was chosen to be three months, because patients with CRC revisited the hospital outpatient clinic three months after the operation. The follow-up coverage was one hundred per cent.

4.1.3.   Elderly patients with rectal cancer (III)

During 2003-2006, a total of 274 rectal cancers were diagnosed in the area of Turku University Hospital. The patients were divided into those aged under 75 years (n=181) and those aged 75 years or older (n=93) at the moment of diagnosis. These agegroups were compared with each other.

All patients had histologically proven adenocarcinoma of the rectum with the lowest border of the tumour located within 15 cm from the anal verge. Patient and tumour characteristics are shown in Table 4.

Table 4. Patient and rectal tumour characteristics according to age (Study III).

	Aged ≥75 (n=93)	Aged<75 (n=181)	P
Gender: M/F	48/45	116/65	
Age (range)	83 (75-100)	63 (34-75)	
Level of tumour			n.s.
upper rectum (11-15 cm)	42 (45%)	86 (48%)	
middle rectum (7-11cm)	33 (35%)	58 (32%)	
lower rectum (0-7cm)	13 (14%)	37 (20%)	
could not be estimated	5 (5%)		
Tumour classification			n.s.
stage 1 (T1-2N0M0)	19 (25%)	35 (20%)	
stage 2 (T3-4N0M0)	21 (27%)	58 (32%)	
stage 3 (T1-4N1-2M0)	25 (32%)	50 (28%)	
stage 4 (M1)	12 (16%)	36 (20%)	
could not be classified	16	2	
Number of lymph nodes (range)	11(0-29)	10 (0-25)	n.s.
Comorbid diseases (important in relation to operative treatment or anesthesia)			
no comorbid diseases	25 (27%)	96 (53%)	<0.001
two ore more comorbid diseases	31 (33%)	27 (15%)	<0.001
cardiac disease	35 (38%)	19 (10%)	
hypertension	18 (19%)	30 (17%)	
cerebrovascular disease	5 (5%)	6 (3%)	
chronic obstructive pulmonary disease	1 (1%)	7 (4%)	
diabetes mellitus	10 (11%)	12 (7%)	
dementia	8 (9%)	3 (2%)	

Reproduced with the permission of the copyright holder

The follow-up data was collected at postoperative control visits during 1-3 years after the diagnosis. Patient and tumour characteristics, the treatment modalities chosen and any complication if noted were recorded. The

information about comorbid diseases was collected with special reference to the importance of the disease in relation to operative treatment or anaesthesia.

4.1.4.   Patients with rectal cancer - special interest in QoL (IV)

During 2005-2008, a total of 150 patients with histologically proven rectal cancer underwent either APR or AR at Turku University Hospital. The intention was to give a QoL questionnaire to all patients undergoing a radical operation for rectal cancer. Many patients declined to participate due to the intimate questions, a few patients were not Finnish speaking and some patients did not complete the questionnaires preoperatively eliminating the comparison between pre- and postoperative QoL scores. Seventy-four radically operated patients answered the preoperative questionnaire. Four patients died during the first postoperative year. One patient with HNPCC underwent colectomy and was thus excluded from the analysis. Three patients had metastases after one year of operation.

At the one year follow-up, 66 patients (33 females and 33 males; mean age 68 years, range 42-86) out of the 69 patients, who met the inclusion criteria, were alive without any sign of recurrent disease. Out of these 66 patients all but one (98%) patient completed the second questionnaire. Forty-four of these patients had undergone AR and a side-to-end anastomosis was used in 40 out of these 44 cases. Twenty-two patients had undergone APR. Patient and tumour characteristics related to both operations are presented in Table 5. There were no significant differences between the operation groups regarding age, gender or tumour stage. Thirty-two patients (46%) did not receive preoperative radiotherapy due to upper third rectal tumour, stage I tumour or earlier pelvic radiotherapy (Table 5). The postoperative complication rate did not differ between the operation groups.

There were no significant differences between patients who did not participate (n=76) and those who participated (n=74) in the study regarding age, tumour stage, the operation (APR vs. AR) or mortality within the first postoperative year.

Table 5. Patient and rectal tumour characteristics according to operation (n=69) (Study IV).

	AR (N=47)	APR (N=22)	P
Gender: M/F	21/26	12/10	n.s.
Age (range)	73 (42-86)	72 (44-84)	n.s.
Level of tumour			<0.001
upper rectum (11-15 cm)	10 (21%)	0	
middle rectum (7-11cm)	19 (40%)	0	
lower rectum (0-7cm)	18 (39%)	22 (100%)	
Tumour classification			n.s.
stage I (T1-2N0M0)	10 (21%)	5 (23%)	
stage II (T3-4N0M0)	21 (45%)	7 (32%)	
stage III (T1-4N1-2M0)	16 (34%)	10 (45%)	
stage IV(M1)	0	0	
Preoperative radiotherapy			0.004
no radiotherapy	27 (57%)	5 (23%)	
short course (25Gy)	13 (28%)	10 (45%)	
long course (50Gy)			
chemoradiation	7 (15%)	7 (32%)	
AR = anterior resection; APR = abdominoperineal resection			

4.2.   Methods

4.2.1.   Preoperative evaluation

The diagnosis of CRC was made from biopsies taken at colonoscopy (studies I, III-IV). In study II, there were some emergency operations, where CRC diagnosis was done postoperatively from the removed tumour or from biopsies taken during surgery.

In all the studies the preoperative staging of CRC was evaluated with whole body CT. The local staging of rectal cancer was completed by DRE and MRI. ERUS was not used.

4.2.2.   **Surgical procedures**

The main principle in all patients with colon cancer (study II) was to carry out a radical surgical operation by making a complete resection of the bowel segment containing the tumour with the draining lymph nodes with distal and proximal margins of at least 5-10 cm. If radical operation was not possible, palliative procedures were carried out at laparotomy (Table 3).

Patients with rectal cancer were operated by doing AR or APR with TME (studies II-IV) or by local excision or some palliative operation such as application of SEMS or stoma (I-III). In case of low AR a diverting stoma was generally favoured, but the surgeon made the final decision during the operation. The intersphincteric or cylindrical abdominoperineal excision techniques were not used.

A combined endoscopic and fluoroscopic approach was used in all stent procedures (study I, III). The guidewire was introduced under direct vision into the stricture and above it through an endoscope. The correct position of the guidewire was verified fluoroscopically. In the majority cases (n=23) the endoscope was withdrawn leaving only the guidewire through the stricture. The stent delivery system was then advanced over the guidewire above the tumour and the endoscope reintroduced beside the stent delivery system. The stent was opened under endoscopic direct vision and fluoroscopic control. In the rest cases (n=3) the stent delivery system was inserted through the endoscope and the stent was then released under endoscopic and fluoroscopic control. Two different uncovered stents were used. Stent selection was based mainly on the location of the stricture; the Ultraflex Precision ™ stent was preferred in distal tumours and the Hanarostent ™ in proximal tumours. Ultraflex Precision ™ stents were inserted by the side of an endoscope and Hanarostent ™ through an endoscope (Figure 5). At the time we started SEMS procedures in 2003 the working channel of our endoscope was too narrow to allow stenting through an endoscope and therefore Ultraflex Precision ™ stents also had to be used for stenting of sigmoid tumours at that time.
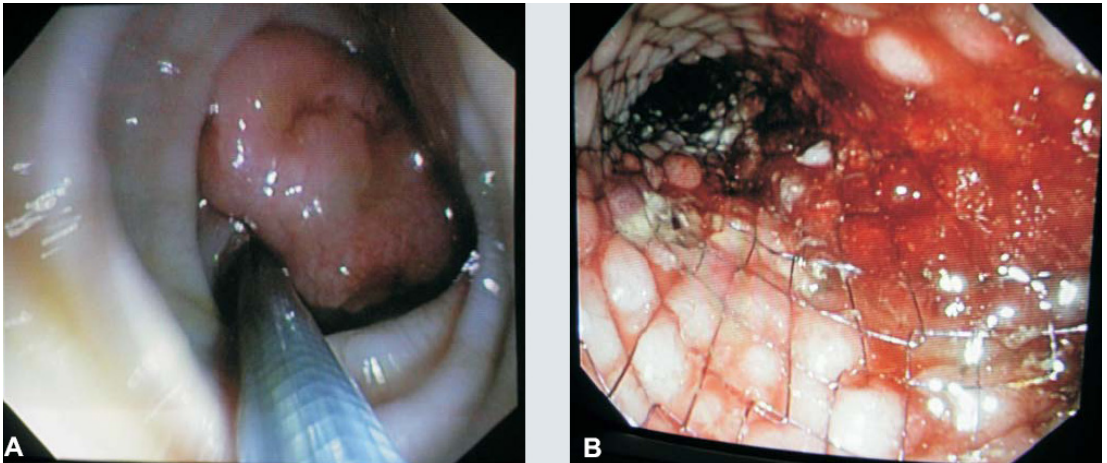
Figure 5. Through the endoscope stenting procedure.A) The stent delivery system is introduced through the tumour B) The stent has just been opened under endoscopic control.

4.2.3. Adjuvant treatment

Preoperative radio- or radiochemotherapy was routinely offered to patients with T3 or T4 rectal cancer in the low- or midrectum (studies II-IV). The standard radiotherapy was a short course treatment (25Gy in 5Gy fractions over 5 days). For locally fixed tumours the long course radio- or radiochemotherapy was used (50.4Gy in 1.8Gy fractions 5-6 weeks). The operation was performed within one week after the short course and 5-8 weeks after the long course treatment.

In all studies, postoperative adjuvant treatment was offered to patients without severe comorbidities with stage III or IV tumour or stage II tumour with additional risk factors.

4.2.4. Histological grading

All tumours were histologically proven adenocarcinomas, which were classified according to TNM classification based on whole body CT, operative findings and histopathological examination (studies II-IV). The operation was considered radical if no visible tumour was left behind and histopathological specimens showed tumour-free distal margins and no metastatic disease on surgery or radiography.

4.2.5. Diagnosis of thromboembolic complications

All patients with a clinical suspicion of DVT or PE underwent radiological investigations: spiral computed tomography for diagnosing PE and sonography for diagnosing DVT.

4.2.6. Quality of life assessment

The QoL was measured with a validated Finnish version (Aalto *et al.* 1999) of the RAND 36-item health survey QoL questionnaire (Hays *et al.* 1993). RAND-36 is a multidimensional questionnaire consisting of 36 questions that assess eight dimensions of health from the patient's viewpoint. These dimensions measure role limitations as a result of physical (RP) or emotional problems (RE), physical functioning (PF), energy and vitality (EV), mental functioning (MF), social functioning (SF), body pain (BP) and general health perception (HP). The scoring scale ranges from 0 to 100, with high scores indicating a high level of functioning and good QoL. The RAND-36 has been validated for use in postoperative patients and its reliability have been proven (Ware *et al.* 1998).

Functional outcome was measured with a self-administered, disease-related questionnaire. Anorectal symptoms included defecation frequency, presence of hard stools, diarrhea, the use of laxatives, difficult evacuation and anal incontinence. Urinary symptoms included incomplete bladder emptying, urgency, dysuria and incontinence. Questions on satisfaction with sex life and dyspareunia were asked in both genders. In men, sexual problems were divided into erectile (impotence and need of medication to improve erection) and ejaculatory dysfunction (missing or retrograde ejaculation). Pelvic pain after the operation was evaluated by symptom frequency and the effect on the patient's daily life.

4.2.7. Statistics

Study I was an observational study.

Statistical analysis in study II was performed using 95% confidence interval.

In study III categorical variables are presented using frequencies and percentages and were compared between groups with the Chi-square test or Fisher's exact test when appropriate. Continuous variables are presented as medians and interquartile ranges and were compared between groups with the Mann-Whitney`s U test.

In Study IV continuous variables were characterized using medians and ranges and in case of categorical variables frequencies and percents were used. The associations between categorical variables were statistically tested using Pearson's chi-squared test and the differences between time-points in categorical variables were tested using McNemar's test (variables with two classes) or Bowker's test of symmetry (variables with more than two classes). Difference of mean age between the operation groups was tested using independent samples t-test. When parametric analyses were appropriate, differences in QoL between time-points, operation groups, anorectal, urinary and sexual dysfunction groups were analysed using repeated measurements ANOVA (PF, EV, HP). In case of non-normal distributions of residuals nonparametric methods were used for analyses (RP, RE, MF, SF, BP). Differences in QoL between the operation groups were tested using Mann-Whitney`s U –test and differences between time-points were tested using Wilcoxon signed rank test. The differences in QoL between anorectal, urinary and sexual dysfunction groups were tested separately in baseline and one year using Mann-Whitney U -test. Bonferroni's method was used to correct the p-values when appropriate.

Statistical analyses were performed using SAS System for Windows, Version 9.2 (SAS Institute Inc, Cary, NC, USA). P-values less than 0.05 were considered statistically significant.

5. RESULTS

5.1. Palliative colonic stenting (I)

Insertion of SEMS was technically successful in 19 (73 %) of the 26 patients with malignant colorectal obstruction (Table 6). Two stents were inserted in one of the patients because of technical problems encountered during the procedure. Seven insertions failed, because a guidewire could not be passed through the stricture. Colostomy was done for five of these patients, ileostomy for one and one patient underwent resection of the primary tumour.

There were three (16 %) colonic perforations related to stent application (Table 6). All the tumours of these patients were located at the sigmoid area (about 20-30 cm proximally to the anus). The Ultraflex Precision ^{TM} stent was used in all these cases. Predilatation was not used. All these three patients died within one week after the insertion of SEMS. At autopsy, the cause of death was bowel perforation at the location of the tumour in all three cases.

Clinical success was achieved in all of the remaining 16 patients (84 %; Table 6). Later complications related to SEMS occurred in three patients: two patients with very low tumour suffered from intensive rectal pain and one had bleeding from the tumour. Both patients with intensive pain needed opiate pain medication, the patient with bleeding needed blood transfusions, but nobody needed surgical procedures. There were neither migrations nor reocclusions of successfully inserted stents.

Table 6. Details of patients with malignant colorectal obstruction and results of insertion of SEMS.

Patient No.(gender/age yr)	site of obstruction	stent	technically successful	clinically successful	complication	subsequent operation
1 (M/45)	middle rectum	UP	+	+	no	
2 (F/66)	middle rectum	UP	+	+	rectal pain	
3 (M/54)	sigmoid	UP	-		no	colostomy
4 (F/57)	sigmoid	UP	+	+	no	
5 (F/57)	sigmoid	UP	+	+	rectal pain	
6 (F/85)	sigmoid	UP	+	-	perforation	
7 (F/62)	sigmoid	UP	+	+	no	
8 (M/55)	proximal rectum	UP	-		no	colostomy
9 (F/68)	sigmoid	UP	-		no	ileostomy
10 (M/81)	middle rectum	UP	+	+	no	
11 (M/84)	proximal rectum	UP	+	+	no	
12 (M/69)	sigmoid	UP	+	+	no	
13 (F/80)	sigmoid	UP	+	+	no	
14 (M/73)	sigmoid	UP	+	-	perforation	
15 (F/73)	sigmoid	UP	-		no	colostomy
16 (M/75)	proximal rectum	UP	+	+	no	
17 (M/67)	sigmoid	UP	+	+	no	
18 (M/81)	sigmoid	UP	+	+	bleeding	
19 (M/77)	sigmoid	UP	+	-	perforation	
20 (F/67)	sigmoid	UP	-		no	resection
21 (M/74)	distal rectum	UP	+	+	no	
22 (M/39)	sigmoid	UP	-		no	colostomy
23 (M/83)	ascending colon	H	+	+	no	
24 (M/72)	sigmoid	H	+	+	no	
25 (M/72)	middle rectum	UP	-		no	colostomy
26 (M/64)	sigmoid	H	+	+	no	
UP= Ultraflex Precision ^{TM} , H = Hanarostent ^{TM} ,+= yes, -= no						

Reproduced with the permission of the copyright holder

5.2.   Thromboembolic complications (II)

Among the 494 cancer patients who underwent colorectal surgery, there were only three (0.6%; 95% confidence interval 0.1 - 1.8%) symptomatic VTEs during the three-month postoperative follow-up period (Table 7). One of the patients presented with PE and two had DVT. The patient with PE also had a tumour in the right lung compatible with pulmonary cancer. One of the patients with DVT had metastatic rectal cancer and the other had a tumour in the ascending colon. The PE manifested 16 days and the DVTs 63 and 78 days after surgery. Among a total of 173 patients with rectal cancer, only one (0.6%) had a DVT after the operation.

The 30-day mortality after surgery was 1.6 % (eight patients) in the study population. Autopsy was performed in four cases. The cause of death was myocardial infarction in two patients, multiorgan failure in one patient and sepsis in one. In the remaining four cases, an autopsy was not performed and the exact cause of death of these four patients can not be definitely known, but in the death certificate it was speculated to be CRC.

Table 7. Characteristics of the patients with thromboembolic event.

patient number	1	2	3
age (years)	92	68	80
tumour site	caecum	ascending colon	rectum
tumour stage	T3N0M0	T3N1M0	M1
operation	JFB30	JFB30	JFF26
duration of prophylaxis (days)	13	10	12
event	PE	DVT	DVT
occurred on postoperative day	16	78	63
JFB30= right hemicolectomy, JFF26= laparotomy and sigmoidostomy PE =pulmonary embolism, DVT= deep venous thrombosis			

5.3. Elderly patients with rectal cancer - special considerations (III)

The stage and the location of the tumour, the number of lymph nodes analysed and the duration of hospital stay (mean 11 vs. 10 days) were similar in the two age groups (Table 4). In the elderly group more concomitant diseases significant for anaesthesia or surgery were encountered and in the younger group preoperative radiation was given more often (67% vs. 27%). Concomitant diseases and metastasized tumours were more common in those who were not operated or had a minor operation than in those who underwent a major operation (concomitant disease 63% vs. 52%, P=0.01, and metastasized disease 36% vs. 12%, P<0.01).

Of the total of 274 patients with rectal cancer, 243 (89%) underwent operative treatment. The percentage of the patients operated was higher (P=0.03) in the younger group (92%) than in the older group (83%). Similarly, ARs or APRs were performed more often in the younger group (71% vs. 56%, P=0.01). Only few local excisions were done in both groups. Palliative procedures, such as applications of SEMS and stoma, were performed equally in both groups. In the patients with AR diverting stoma was constructed to the same (n.s.) percentage of patients in the older (42%) and younger (56%) group. If diverting stoma was constructed it was closed uniformly in both groups. Only one diverting stoma in each group remained permanently. Postoperative adjuvant chemotherapy was given more often to younger than older patients (60% vs. 24%).

The overall mortality rate within one month after diagnosis in the whole study population was 3% (9/274). Only two (1 vs. 1 patient) of these nine patients had been operated (Table 8). Both of the operations were radical: the older patient underwent local excision and the younger patient AR. The older patient died of iatrogenic intra-abdominal perforation and the younger patient died of anastomotic leak.

Altogether, 62 (26%) patients developed postoperative complications (Table 8). There was no statistically significant difference between the age groups in the percentage of patients with complications after all operations (34% in the older and 22% in the younger group, p=n.s.), after ARs (29% vs. 17%, p=n.s.) or after APRs (46% vs. 31%, p=n.s.). The most common complication after APR was infection of the perineal wound, which seemed to be slightly more common after preoperative radiation in both groups although the differences did not reach statistical significance. In the younger group there were five clinical anastomotic leakages, two of which had to be operated, while three leakages were treated conservatively. In the elderly group there were no clinical anastomotic leakages.

Table 8. Postoperative 30-day mortality and complications after operations for rectal cancer.

	Aged ≥ 75 (n=77)	Aged < 75 (n=166)	P
30-day mortality	1 (1%)	1 (1%)	n.s.
complication			
complication after all operations	26/77 (34%)	36/166 (22%)	n.s.
complication after anterior resection	8/28(29%)	13/77 (17%)	n.s.
complication after abdominoperineal resection	11/24 (46%)	16/52 (31%)	n.s.
Anastomotic leakage	0	5 (3%)	
Postoperative bleeding	1 (1%)	0	
Infections			
Abdominal wound	2 (3%)	4 (2%)	
Perineal wound	7 (9%)	10 (6%)	
Intra-abdominal abscess	0	4 (2%)	
Sepsis	1 (1%)	1 (1%)	
Pulmonary complication	1 (1%)	1 (1%)	
Cardiac complication	3 (4%)	2 (1%)	
Thromboembolic complication	0	1 (1%)	
Genitourinary complication	5 (6%)	4 (2%)	
Stomal complication	1 (1%)	2 (1%)	
Other	5 (6%)	2 (1%)	

Reproduced with the permission of the copyright holder

5.4.   Anorectal, urinary and sexual dysfunction (IV)

No significant differences were found between the preoperative condition and at one year postoperatively in anorectal symptoms of frequency, presence of hard stools, diarrhea and the use of laxatives among patients who underwent AR. Sixteen (36%) of AR operated patients had major anal dysfunction such as anal incontinence, urgency, daily constipation or frequency > 5 times per day after one year, but 15 (34%) patients reported of these symptoms already preoperatively (P=0.786). Patients with preoperative radiation suffered from more severe anal incontinence than those without preoperative radiation (P=0.012). When AR operated patients were asked about whether defecation related symptoms disturb their daily life, these patients reported worsened symptoms at one year after surgery compared to the preoperative status (P=0.01).

Thirty-three (51%) patients reported some kind of urinary dysfunction at one year postoperatively, but 27 (42%) patients also reported these symptoms preoperatively. There was no significant difference between such urinary symptoms as incomplete bladder emptying, urgency or dysuria, but urinary incontinence worsened (P=0.026) at one year after surgery. Patient's gender had no significant impact on urinary incontinence (7 females, 6 males). The incidence of dysuria was higher after an APR procedure compared with an AR operation (P=0.001). Preoperative radiation seemed to be associated with incomplete bladder emptying (P=0.076), although the difference did not reach statistical significance.

Fifty-six (86%) patients (30 males, 26 females) answered the questions regarding their sex life. Out of these 56 patients, 48 (86%; 26 males and 22 females) were sexually active preoperatively. Twelve women (46%) were satisfied with their sex life preoperatively and 10 (38%) after surgery (P=0.531). Twenty men (67 %) reported satisfactory preoperative sex life, but only 11 men (37 %) were satisfied postoperatively (P=0.039). Sexual dysfunction was measured by the absence of ejaculation or the presence of retrograde ejaculation, impotence and need of medication to improve erection. Seventeen men (57%) reported sexual dysfunction preoperatively and 21 (73%) at one year follow-up. There was a trend towards worsened sexual function (P=0.06). Male patients with preoperative radiation had more problems with ejaculation (P=0.028). Male patients with sexual dysfunction (n=21; 2 answers missing) were also asked to state their own opinion regarding the cause of sexual dysfunction; four men referred to physical problems and three to emotional problems, while the remainder (n=12) of them found no association between their sex life disturbances and their disease or its operative treatment.

5.5.   Quality of life after operation for rectal cancer (IV)

Patients reported similar general QoL at one year after surgery compared with preoperative general QoL and mental functioning was even better postoperatively (P<0.001) (Figure 6). There was no difference in the QoL between the operation groups. Preoperative radiation had no influence on QoL. In QoL analysis, problems with physical functions were associated with anal dysfunction after AR (P<0.001). Social function was worsened in patients having urinary dysfunction one year after the operation (P=0.038). Sexual dysfunction did not cause statistically significant worsening of QoL in any dimensions.
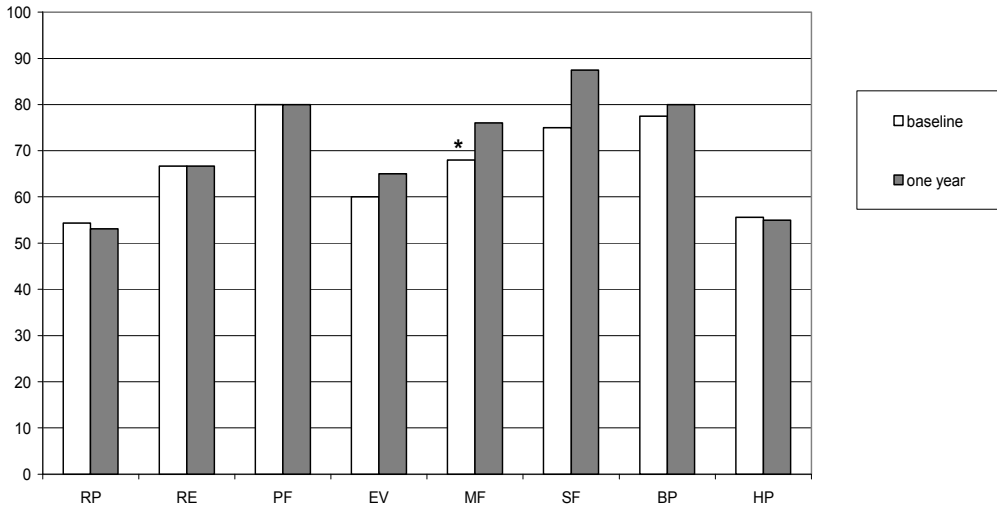
Figure 6. Quality of life in patients with rectal cancer surgery preoperatively and at one year postoperatively (n=69 and n=65, respectively) (The median values of different RAND-36 QoL scores).

RP=role limitations as a result of physical problems; RE=role limitations as a result of emotional problems; PF=physical functioning; EV=energy and vitality; MF=mental functioning; SF=social functioning; BP=body pain; HP=general health perception
(* = statistically significant).

6. DISCUSSION

6.1. General discussion

Recent developments in various treatment modalities in CRC, such as surgical and endoscopic techniques and adjuvant treatments, have decreased morbidity and mortality in patients with colon and especially with rectal cancer (Folkesson *et al.* 2005; Heald and Ryall 1986; Hotta *et al.* 2007). In the present work, the aim was to study the feasibility, safety and efficacy of the surgical treatment in patients with CRC. Studies were conducted with special interest in controversial issues: stenting as a palliative procedure for metastasized CRC, duration of thromboprophylaxis after the surgical treatment of CRC, treatment of the increasing population of elderly people as well as QoL and anorectal-, urinary- and sexual dysfunction after the treatment of rectal cancer.

We found that stenting provides an alternative to palliative surgery in the treatment of malignant colorectal obstruction. However, perforation is a dangerous complication of the procedure. Low molecular heparin given for a median of 11 days until hospital discharge seems to provide sufficient thromboprophylaxis after surgery for CRC combined with the use of graded compression stockings and early mobilization. Aging is often associated with concomitant diseases, which affects the choice of the treatment modality in patients with CRC. However, in selected patients aged over 75 years even major surgery for rectal cancer can be done with morbidity and mortality rates comparable to those in younger patients. General QoL seems to be similar preoperatively and postoperatively. Postoperative pelvic dysfunction was associated with an impaired QoL in some dimensions.

Many factors related to the patient and the disease must be taken into account when making treatment decisions in CRC to ensure successful treatment of CRC, patient satisfaction and QoL.

6.2. Study material and methods

6.2.1. Stenting procedure

The amount of patients in study I was only 26, which causes some limitations when drawing conclusions. The follow-up time of some patients was short.

At the time SEMS procedures began in our institute in 2003 the working channel of our endoscopes was too narrow to allow stenting through an endoscope and therefore Ultraflex Precision ™ stents also had to be used for stenting sigmoid tumours. The Ultraflex Precision ™ stent delivery system is quite stiff and aimed only for distal stenting. Therefore, it was difficult to safely

advance to proximal strictures. The lack of a suitable endoscope for through-endoscope stenting can increase the amount of perforations.

6.2.2. Thromboembolic complications

A limitation of study II was that it was retrospective. Patient data was collected from the electronic archives of all diagnostic departments of all hospitals situated within the hospital district of southwest Finland and analyzed for up to three months after the operation with special reference to the occurrence of clinical and symptomatic VTE. It is possible that some thromboembolic complications have been treated in some other hospitals and thus missed.

Autopsy was performed in only half (4/8) of the cases. Therefore, it can not be totally excluded that within the other half there may have been thromboembolic complications. However, the patients who were not autopsied suffered from metastatic cancer and had no clinical symptoms suggesting thromboembolic events such as PE.

6.2.3. Measuring the quality of life

The weakness of study IV was the relatively small number of patients in subgroups resulting in an underpowered comparison. More significant differences might have been found in larger patient series and by using more detailed, validated questionnaires for urinary, anorectal and sexual dysfunction. The RAND-36 questionnaire has also been shown to underestimate the effect of sexual dysfunction on the overall QoL (Ware *et al.* 1998).

6.3. Morbidity and mortality

Recent developments in various treatment modalities of rectal cancer such as surgical and endoscopic techniques and adjuvant treatments have decreased morbidity and mortality in patients with rectal cancer (Folkesson *et al.* 2005; Heald and Ryall 1986; Law *et al.* 2006; Strohlein *et al.* 2008). In earlier studies, postoperative mortality after CRC operation has ranged from 0% to 12% and morbidity from 12% to 40% (Ascanelli *et al.* 2003; Hohenberger *et al.* 2003; Law and Chu 2004). Thus, our results on the overall mortality rate of 3% (study III), and the 30-day mortality after major surgery for CRC ranging from 1% to1.6 % (studies II-III) are satisfactory. In contrast the mortality rate of 16 % after palliative stenting procedure for obstructive CRC (study I) is high compared to earlier studies, which have reported stent-related mortality rates as low as <1% (range 0-0.58%) (Sebastian *et al.* 2004). The morbidity rate 22-34% after all operation modalities for rectal cancer is reasonable (study III).

6.4.   **Palliative colonic stenting**

According to the earlier literature, the technical success rate of colonic stenting in the palliative indication ranges between 64 % and 100 % and the clinical success rate between 46 % and 100 % (Sebastian *et al.* 2004; Watt *et al.* 2007). The results of the present study (73% and 84%, respectively) are consistent with earlier results in this respect.

In earlier studies (Law *et al.* 2004; Suzuki *et al.* 2004; Watt *et al.* 2007), the complication rate related to stent application ranged from 25 % to 40 %, with most complications being minor. Perforation of the bowel is the most dangerous complication. Perforations related to stent placement have been reported on an average in 4 % of the cases (Crosta *et al.* 2006; Sebastian *et al.* 2004). The perforations are related to the guidewires, balloon dilatation and expansion of the stent (Camunez *et al.* 2000; Sebastian *et al.* 2004). Predilatation may increase the rate of perforations (Sebastian *et al.* 2004). In our material there were three (16 %) colonic perforations related to stent application. All these three perforations involved the use of the Ultraflex Precision [TM] colonic stent system in which SEMS was inserted by the side of an endoscope under fluoroscopic guidance. Predilatation was not used. The main reasons for this relatively large number of perforations in our material were very probably the lack of a suitable endoscope for through-endoscope stenting at the time of the first stenting procedures and the beginning of the learning curve.

Perforation may also be a more common complication than reported earlier. A previously conducted randomized trial comparing surgery with stenting for incurable left-sided malignant colonic obstruction had to be stopped because of an unexpectedly high number of perforations, also late perforations, in the stented group (van Hooft *et al.* 2008).

Minor complications such as migration of the successfully inserted SEMS (12%) and obstruction after stenting (7 %) have been reported earlier (Sebastian *et al.* 2004; Watt *et al.* 2007). In the current study, neither migrations nor obstructions occurred after stenting although all patients had clinical symptoms of obstruction before stenting and sixteen of the strictures could not be passed by endoscope. It is probable that the lack of stent migrations is associated with the tightness of the strictures in the present patient material involving only cases with obstruction, widespread disease and few further oncologic treatments. Stent migration is frequently seen in marked tumour responses with oncologic treatments. The follow-up time of some of the patients was also short which may have affected on the results.

6.5.   Thromboembolic complications

Abdominal surgery for CRC has been classified as a high-risk procedure for VTE and thromboprophylaxis is strongly recommended (Geerts *et al.* 2008). Even despite thromboprophylaxis with LMWH for the first postoperative week, the rate of late VTE has been reported to be as high as 10-20 % (Rasmussen *et al.* 2003). In our study, the patients were treated with LMWH until hospital discharge (median 11 days) and there were only three symptomatic (0.6%) thrombotic complications among 494 consecutive patients undergoing abdominal surgery for CRC and only one (0.6%) thrombotic complication after 173 laparotomies for rectal cancer. All these three patients survived.

Our good results may be associated with the fact that our protocol is to continue the thromboprophylaxis during the whole hospitalization until proper mobilization, which in the elderly and those in poor general condition generally takes longer than in younger patients. Thus at our institution patients at the highest risk for VTE receive thromboprophylaxis for much longer than those at lower risk.

The failure to prevent VTE results in an increased risk of post-thrombotic syndrome. After symptomatic DVT of the lower extremities, 30 % of the patients will develop the post-thrombotic syndrome within 2 years and 20 % of these are severe (Pesavento *et al.* 2006). On the other hand, there was no increase in the risk of the post-thrombotic syndrome after asymptomatic proximal or distal DVT after total knee or hip arthroplasty during a minimum follow-up of seven years (Lonner *et al.* 2006). Criticism has ,thus, been raised regarding the use of an asymptomatic thromboembolic event as an end point when investigating thromboprophylaxis (Odonnell and Kearon 2007). Although some association between asymptomatic DVT and the development of symptomatic VTE an PE has been reported (Geerts *et al.* 2008; Mismetti *et al.* 2001), the true benefit to the patient of reducing asymptomatic thrombosis is at present unclear and remains to be established.

6.6.   Elderly patients with rectal cancer

Exact preoperative risk assessment, careful selection of patients for major surgery, standardized surgical techniques and improved perioperative care are essential in keeping morbidity and mortality rates acceptable with elderly CRC patients (Vironen *et al.* 2004). In the present study the complication rate was the same in two age groups after major surgery, which is very probably associated with patient selection, so that elderly patients with poor general condition or severe comorbidity were more often considered unfit for major surgery.

Compliance with preoperative radiotherapy is also good in elderly patients. Toxicity rates and benefit in terms of prevention of local recurrences seem to be similar in older and younger patients in randomised trials (Folkesson *et al.* 2005; Martijn and Vulto 2007; Peeters *et al.* 2007). In these trials it has been shown that preoperative radiotherapy is beneficial for cancer-specific survival and local recurrence rates after long-term follow-up, while overall survival was not improved after preoperative radiotherapy in the older group or younger group. In the present study, preoperative radiotherapy was given more often in the younger group than in the older group because of comorbid diseases and also partly because of age itself. Although survival is the most important endpoint of any cancer treatment, especially in rectal cancer the avoidance of local recurrences, causing a very negative impact on the quality of life, is also important. Therefore, in our series, elderly patients may have been underrepresented in the group of patients to whom preoperative radiotherapy was offered.

In the present study, adjuvant chemotherapy and postoperative radiotherapy were offered to patients without severe comorbidity with stage III or IV tumour or stage II tumour with some additional risk factors. Younger patients with rectal cancer were more often evaluated to be suitable for oncological treatment. Although recent studies (Kosmider and Lipton 2007; Ptok *et al.* 2006; Tournigand *et al.* 2006) have shown that adjuvant treatment is feasible and beneficial for elderly patients without significant comorbidity, in real life many elderly patients still do not receive this treatment because of comorbidity and their poor general wellbeing.

6.7. Anorectal, urinary- and sexual dysfunction after operation for rectal cancer

Major anal dysfunction (urgency, frequency, incontinence or constipation) occurred in 30-70 % of patients after AR (Vironen *et al.* 2006). In our study 16 (36%) of AR operated patients had major anal dysfunction at one year after the operation. There was no statistically significant difference in the occurrence of pre- and postoperative bowel dysfunction. This may be explained that the completion of the first questionnaire was immediately before surgery and at that time the patients suffered from anorectal dysfunction caused by their rectal tumour. Comparable to the earlier studies (Jess *et al.* 2002; Vironen *et al.* 2006), the patients with a permanent stoma have a similar QoL as AR operated patients.

Permanent major urinary dysfunction has been rare after the introduction of nerve preserving TME technique for rectal cancer surgery. However, the

incidence of minor urogenital dysfunction has decreased slightly and the incidence varies between 0-40% (Bohm *et al.* 2008; Moriya 2006; Nesbakken *et al.* 2000). In our study 33 (51%) patients reported some kind of urinary dysfunction at one year postoperatively, but 27 (42%) patients reported these symptoms already preoperatively. Postoperative urinary incontinence has been reported to be associated with preoperative incontinence and female sex (Lange *et al.* 2008). In our study urinary incontinence worsened at one year after operation, but was not associated with gender.

Eighteen patients (27%) in this study were either sexually inactive or were unwilling to answer the questions about sex life and therefore could not be evaluated for sexual function. After rectal cancer surgery, impotence rates range from 20% to 46%, and 20%-60% of potent patients are unable to ejaculate (Moriya 2006). In our study 21 (73%) males reported sexual dysfunction one year postoperatively, but 17 (57%) males reported this already preoperatively. At one year follow-up there was a trend towards worsened sexual function, but statistical significance was not reached. Male patients with sexual dysfunction (n=21, 2 answers missing) were also asked to state their own opinion regarding the cause of sexual dysfunction; four men referred to physical and three to emotional and the remainder (n=12) of the men found no association between their sex life disturbances and their disease or its operative treatment. This is in line with the earlier finding of the multifactorial nature of sexual dysfunction after surgical treatment of rectal cancer (Hendren *et al.* 2005). In the current study female patients reported no changes in their sex life after surgery for rectal cancer. Information on female sexual function is not as easily obtained, but according to earlier reports also women seem to have some sexual problems following rectal cancer surgery (Bohm *et al.* 2008).

Preoperative short course radiotherapy has been shown to cause increased risk for urinary dysfunction (Pollack *et al.* 2006), impaired anorectal function (Murata *et al.* 2008; Pollack *et al.* 2006) and increase the incidence of sexual dysfunction (Hendren *et al.* 2005). However, there are also controversial reports in the literature regarding the issue, (Pietrzak *et al.* 2007; Pietsch *et al.* 2007). In the present study, preoperative radiation was associated with more severe anal incontinence, and in male patients with problems of ejaculation. Similarly, there was a trend towards impaired bladder emptying in patients who underwent preoperative radiation therapy.

6.8.   Quality of life after operation for rectal cancer

There was no difference between preoperative and postoperative general QoL and mental functioning was even better postoperatively. Postoperative pelvic dysfunction was associated with an impaired QoL in some dimensions: social

functioning associated with urinary dysfunction after both AR and APR operations and physical functioning with anorectal dysfunction after AR, which has also been reported earlier (Vironen *et al.* 2006). Sexual dysfunction did not impair QoL in our study, which may be influenced by the relatively weak correlation between sexual function and RAND-36 possibly underestimating the overall effect of sexual dysfunction on QoL (Ware *et al.* 1998).

The explanation of the similarity of preoperative and postoperative general QoL and better postoperative mental functioning may be preoperative symptoms and distress in addition to the "response shift" phenomenon at one year after the operation. The "response shift" means that patients who have survived a life-threatening disease, seem to develop a conscious awareness leading to positive appreciation of everyday life (Rauch *et al.* 2004).

The type of surgery did not have a significant impact on QoL, which is in line with earlier studies that used the RAND-36 questionnaire (Jess *et al.* 2002; Vironen *et al.* 2006).

Pelvic floor function affecting QoL schould be taken into account when making treatment decisions in rectal cancer. Adequate preoperative information is essential in increasing patient tolerance regarding these postoperative symptoms.

7. CONCLUSIONS

The data of the present study led to the following conclusions:

1) SEMS insertion is an effective alternative in the palliative treatment of patients with malignant colorectal obstruction. However, perforation is a dangerous complication related to the procedure.

2) LMWH given for a median of eleven days until hospital discharge seem to provide sufficient thromboprophylaxis after surgery for colorectal cancer, when combined with the use of graded compression stockings and early mobilization.

3) With preoperative selection, considering the comorbidities and the spread of the malignancy, patients over 75 years are suitable for major surgery for rectal cancer with morbidity and mortality rates comparable to those in younger patients.

4) The general QoL of patients with rectal cancer is similar at one year after surgery as preoperatively. Postoperative pelvic dysfunction is associated with an impaired QoL in some dimensions.

8.   ACKNOWLEDGEMENTS

I express my warmest thanks to Erkki Pekkala, MD, PhD, for his support and guidance in gastroenterological surgery and especially in proctology.

I express my great respect to Docent Timo Savunen, the Head of the Department of Surgery, for his positive attitude to scientific research and for the opportunity to work at his clinic.

I am grateful to Docent Jari Ovaska, Docent Risto Gullichsen, Maija Lavonius MD, PhD and Simo Laine, MD, PhD for their supervision and collaboration in gastroenterological surgery. Furthermore, my thanks go to my other colleagues of gastrointestinal surgery for their support and for creating a positive working atmosphere.

I want to thank the personnel at Surgical Word 233 and at Endoscopy Word 226 for tolerating the extra work of carrying out the distribution of questionnaires and for their friendship. My colleagues at the Surgical Department and the personnel at Surgical Words 254, 250, 216, and 227 deserve my warmest thanks for providing a positive atmosphere to work in and for supportive attitude towards my projects.

I want to thank all my friends for enjoyable and unforgettable moments together away from work and science. Special thanks belong to Niina Koivuviita and Tiina Vaari for their giving "women energy" for me during these years.

I express my deepest thanks to all my family members for their continuous support. I especially want to thank my parents Anneli ja Pekka Uskali for their never failing love and encouragement followed me throughout my life.

Finally, this thesis is dedicated to those who matter the most- my husband Anssi and our dear children Heli and Annika.

Turku, February 2010

Pirita Varpe

9. REFERENCES

Aalto A-M, Aro A, and Teperi J. RAND-36 as a measure of health related quality of life. Reality, construct validity and reference values in the Finnish population. National institute for health and welfare 1999; www.stakes.fi

Abir F, Alva S, and Longo WE. The management of rectal cancer in the elderly. Surg Oncol 2004; 13:223-234.

Akbari R, and Wong W. Endorectal ultrasound and the preoperative staging of rectal cancer. Scand J Surg 2003; 92:25-33.

Alcantara M, Serra X, Bombardo J, Falco J, Perandreu J, Ayguavives I, Mora L, Hernando R, and Navarro S. Colorectal stenting as an effective therapy for preoperative and palliative treatment of large bowel obstruction: 9 years' experience. Tech Coloproctol 2007; 11:316-322.

Alizadeh K, and Hyman N. Venous thromboembolism prophylaxis in colorectal surgery. Surg Technol Int 2005; 14:165-170.

Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, and de Gramont A. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004; 350:2343-2351.

Arkenau HT, Bermann A, Rettig K, Strohmeyer G, and Porschen R. 5-Fluorouracil plus leucovorin is an effective adjuvant chemotherapy in curatively resected stage III colon cancer: long-term follow-up results of the adjCCA-01 trial. Ann Oncol 2003; 14:395-399.

Arnold C, Goel A, Blum H, and Boland C. Molecular pathogenesis of colorectal cancer: implications for molecular diagnosis. Cancer 2005; 104:2035-2047.

Ascanelli S, Navarra G, Tonini G, Feo C, Zerbinati A, Pozza E, and Carcoforo P. Early and late outcome after surgery for colorectal cancer: elective versus emergency surgery. Tumori 2003; 89:36-41.

Asoglu O, Matlim T, Karanlik H, Atar M, Muslumanoglu M, Kapran Y, Igci A, Ozmen V, Kecer M, and Parlak M. Impact of laparoscopic surgery on bladder and sexual function after total mesorectal excision for rectal cancer. Surg Endosc 2008; 23:296-303.

Baatrup G, Breum B, Qvist N, Wille-Jorgensen P, Elbrond H, Moller P, and Hesselfeldt P. Transanal endoscopic microsurgery in 143 consecutive patients with rectal adenocarcinoma: results from a Danish multicenter study. Colorectal Dis 2009; 11:270-275.

Ballantyne G, and Quin J. Surgical treatment of liver metastases in patients with colorectal cancer. Cancer 1993; 71:4252-4266.

Bass G, Fleming C, Conneely J, Martin Z, and Mealy K. Emergency first presentation of colorectal cancer predicts significantly poorer outcomes: a review of 356 consecutive Irish patients. Dis Colon Rectum 2009; 52:678-684.

Batignani G, Monaci I, Ficari F, and Tonelli F. What affects continence after anterior resection of the rectum? Dis Colon Rectum 1991; 34:329-335.

Bax TW, and McNevin MS. The value of diverting loop ileostomy on the high-risk colon and rectal anastomosis. Am J Surg 2007; 193:585-587

Benson AB, 3rd, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, Krzyzanowska MK, Maroun J, McAllister P, Van Cutsem E, Brouwers M, Charette M, and Haller DG. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004; 22:3408-3419.

Bentrem DJ, Okabe S, Wong WD, Guillem JG, Weiser MR, Temple LK, Ben-Porat LS, Minsky BD, Cohen AM, and Paty PB. T1 adenocarcinoma of the rectum: transanal excision or radical surgery? Ann Surg 2005; 242:472-477

Bergqvist D. Low molecular weight heparin for the prevention of venous thromboembolism after abdominal surgery. Br J Surg 2004; 91:965-974.

Bergqvist D. Venous thromboembolism: a review of risk and prevention in colorectal surgery patients. Dis Colon Rectum 2006; 49:1620-1628.

Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, and Dietrich-

Neto F. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002; 346:975-980.

Birgisson H, Pahlman L, Gunnarsson U, and Glimelius B. Late gastrointestinal disorders after rectal cancer surgery with and without preoperative radiation therapy. Br J Surg 2008; 95:206-213.

Bittorf B, Stadelmaier U, Gohl J, Hohenberger W, and Matzel KE. Functional outcome after intersphincteric resection of the rectum with coloanal anastomosis in low rectal cancer. Eur J Surg Oncol 2004; 30:260-265.

Bittorf B, Stadelmaier U, Merkel S, Hohenberger W, and Matzel KE. Does anastomotic leakage affect functional outcome after rectal resection for cancer? Langenbecks Arch Surg 2003; 387:406-410.

Bohm G, Kirschner-Hermanns R, Decius A, Heussen N, Schumpelick V, and Willis S. Anorectal, bladder, and sexual function in females following colorectal surgery for carcinoma. Int J Colorectal Dis 2008; 23:893-900.

Borly L, Wille-Jorgensen P, and Rasmussen MS. Systematic review of thromboprophylaxis in colorectal surgery - an update. Colorectal Dis 2005; 7:122-127.

Bosset JF, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Briffaux A, and Collette L. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results--EORTC 22921. J Clin Oncol 2005; 23:5620-5627.

Bretagnol F, Rullier E, Laurent C, Zerbib F, Gontier R, and Saric J. Comparison of functional results and quality of life between intersphincteric resection and conventional coloanal anastomosis for low rectal cancer. Dis Colon Rectum 2004; 47:832-838.

Brown C, Fenech D, and McLeod R. Reconstructive techniques after rectal resection for rectal cancer. Cochrane Database Syst Rev 2008; CD006040.

Brown G, Davies S, Williams GT, Bourne MW, Newcombe RG, Radcliffe AG, Blethyn J, Dallimore NS, Rees BI, Phillips CJ, and Maughan TS. Effectiveness of preoperative staging in rectal cancer: digital rectal examination, endoluminal ultrasound or magnetic resonance imaging? Br J Cancer 2004; 91:23-29.

Buess G, Kipfmuller K, Hack D, Grussner R, Heintz A, and Junginger T. Technique of transanal endoscopic microsurgery. Surg Endosc 1988a; 2:71-75.

Buess G, Kipfmuller K, Ibald R, Heintz A, Hack D, Braunstein S, Gabbert H, and Junginger T. Clinical results of transanal endoscopic microsurgery. Surg Endosc 1988b; 2:245-250.

Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudelko M, Kryj M, Oledzki J, Szmeja J, Sluszniak J, Serkies K, Kladny J, Pamucka M, and Kukolowicz P. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2004; 72:15-24.

Bullard KM, Trudel JL, Baxter NN, and Rothenberger DA. Primary perineal wound closure after preoperative radiotherapy and abdominoperineal resection has a high incidence of wound failure. Dis Colon Rectum 2005; 48:438-443.

Camilleri-Brennan J, and Steele RJ. Quality of life after treatment for rectal cancer. Br J Surg 1998; 85:1036-1043.

Camilleri-Brennan J, and Steele RJ. Prospective analysis of quality of life and survival following mesorectal excision for rectal cancer. Br J Surg 2001; 88:1617-1622.

Camunez F, Echenagusia A, Simo G, Turegano F, Vazquez J, and Barreiro-Meiro I. Malignant colorectal obstruction treated by means of self-expanding metallic stents: effectiveness before surgery and in palliation. Radiology 2000; 216:492-497.

Cappell M. From colonic polyps to colon cancer: pathophysiology, clinical presentation, screening and colonoscopic therapy. Minerva Gastroenterol Dietol 2007; 53:351-373.

Chadwick M, Vieten D, Pettitt E, Dixon AR, and Roe A. Short course preoperative radiotherapy is the single most important risk factor for perineal wound complications after abdominoperineal excision of the rectum. Colorectal Dis 2006; 8:756-761.

Chang G, Rodriguez-Bigas M, Skibber J, and Moyer V. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 2007; 99:433-441.

Chau I, Norman AR, Cunningham D, Tait D, Ross PJ, Iveson T, Hill M, Hickish T, Lofts F, Jodrell D, Webb A, and Oates JR. A randomised comparison between 6 months of bolus fluorouracil/leucovorin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer. Ann Oncol 2005; 16:549-557.

Chautard J, Alves A, Zalinski S, Bretagnol F, Valleur P, and Panis Y. Laparoscopic colorectal surgery in elderly patients: a matched case-control study in 178 patients. J Am Coll Surg 2008; 206:255-260.

Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet 2001; 358:1291-1304.

Crosta C, Trovato C, Fiori G, Ravizza D, Tamayo D, Zampino MG, and Biffi R. Metal stent placement in acute malignant colorectal obstruction. Dig Liver Dis 2006; 38:341-346.

Davies M, Harries D, Hirst G, Beynon R, Morgan A, Carr N, and Beynon J. Local recurrence after abdomino-perineal resection. Colorectal Dis 2009; 11:39-43.

Deans G, Krukowski Z, and Irwin S. Malignant obstruction of the left colon. Br J Surg 1994; 81:1270-1276.

Deans G, Parks T, Rowlands B, and Spence R. Prognostic factors in colorectal cancer. Br J Surg 1992; 79:608-613.

Del Rio C, Sanchez-Santos R, Oreja V, De Oca J, Biondo S, Pares D, Osorio A, Marti-Rague J, and Jaurrieta E. Long-term urinary dysfunction after rectal cancer surgery. Colorectal Dis 2004; 6:198-202.

Dias AR, Nahas CS, Marques CF, Nahas SC, and Cecconello I. Transanal endoscopic microsurgery: indications, results and controversies. Tech Coloproctol 2009; 13:105-111.

Dohmoto M. New Method. Endoscopic implantation of rectal stent in palliative treatment of malignant stenosis. Endosc Dig 1991; 3:1507-1512

Duffy MJ, van Dalen A, Haglund C, Hansson L, Holinski-Feder E, Klapdor R, Lamerz R, Peltomaki P, Sturgeon C, and Topolcan O. Tumour markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines for clinical use. Eur J Cancer 2007; 43:1348-1360.

Edler D, Ohrling K, Hallstrom M, Karlberg M, and Ragnhammar P. The number of analyzed lymph nodes - a prognostic factor in colorectal cancer. Acta Oncol 2007; 46:975-981.

Endreseth BH, Romundstad P, Myrvold HE, Bjerkeset T, and Wibe A. Rectal cancer treatment of the elderly. Colorectal Dis 2006; 8:471-479.

Engel J, Kerr J, Schlesinger-Raab A, Eckel R, Sauer H, and Holzel D. Quality of life in rectal cancer patients: a four-year prospective study. Ann Surg 2003; 238:203-213.

Enker WE. Total mesorectal excision--the new golden standard of surgery for rectal cancer. Ann Med 1997; 29:127-133.

Fazio VW, Zutshi M, Remzi FH, Parc Y, Ruppert R, Furst A, Celebrezze J, Jr., Galanduik S, Orangio G, Hyman N, Bokey L, Tiret E, Kirchdorfer B, Medich D, Tietze M, Hull T, and Hammel J. A randomized multicenter trial to compare long-term functional outcome, quality of life, and complications of surgical procedures for low rectal cancers. Ann Surg 2007; 246:481-488

Feng B, Zheng MH, Mao ZH, Li JW, Lu AG, Wang ML, Hu WG, Dong F, Hu YY, Zang L, and Li HW. Clinical advantages of laparoscopic colorectal cancer surgery in the elderly. Aging Clin Exp Res 2006; 18:191-195.

Finnish cancer registry. Cancer statistic of National institute for Welfare and Health (STAKES) 2007; www.cancerregistry.fi:

Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW, Jr., Hellinger M, Flanagan R, Jr., Peters W, and Nelson H. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. Ann Surg 2007; 246:655-662

Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, and Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005; 23:5644-5650.

Fregonese D, Naspetti R, Ferrer S, Gallego J, Costamagna G, Dumas R, Campaioli M, Morante

AL, Mambrini P, Meisner S, Repici A, Andreo L, Masci E, Mingo A, Barcenilla J, and Petruzziello L. Ultraflex precision colonic stent placement as a bridge to surgery in patients with malignant colon obstruction. Gastrointest Endosc 2008; 67:68-73.

Frykholm GJ, Glimelius B, and Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. Dis Colon Rectum 1993; 36:564-572.

Fucini C, Elbetti C, Petrolo A, and Casella D. Excision of the levator muscles with external sphincter preservation in the treatment of selected low T4 rectal cancers. Dis Colon Rectum 2002; 45:1697-1705.

Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, and Colwell CW. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133:381-453

Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT, Untereiner M, Leduc B, Francois E, Maurel J, Seitz JF, Buecher B, Mackiewicz R, Ducreux M, and Bedenne L. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006; 24:4620-4625.

Glimelius B, Gronberg H, Jarhult J, Wallgren A, and Cavallin-Stahl E. A systematic overview of radiation therapy effects in rectal cancer. Acta Oncol 2003; 42:476-492.

Grossmann I, de Bock GH, Meershoek-Klein Kranenbarg WM, van de Velde CJ, and Wiggers T. Carcinoembryonic antigen (CEA) measurement during follow-up for rectal carcinoma is useful even if normal levels exist before surgery. A retrospective study of CEA values in the TME trial. Eur J Surg Oncol 2007; 33:183-187.

Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, and Brown JM. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 2005; 365:1718-1726.

Gukovsky-Reicher S, Lin RM, Sial S, Garrett B, Wu D, Lee T, Lee H, Arnell T, Stamos MJ, and

Eysselein VE. Self-expandable metal stents in palliation of malignant gastrointestinal obstruction: review of the current literature data and 5-year experience at Harbor-UCLA Medical Center. MedGenMed 2003; 5:16.

Hallbook O, and Sjodahl R. Anastomotic leakage and functional outcome after anterior resection of the rectum. Br J Surg 1996; 83:60-62.

Haller D, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, Hill M, Gilberg F, Rittweger K, and Schmoll HJ. First efficacy findings from a randomized phase III trial of capecitabine + oxaliplatin vs. bolus 5-FU/LV for stage III colon cancer (NO16968/XELOXA study) Proc.ESMO/ECCO. Abstract 2009.

Havenga K, Enker WE, McDermott K, Cohen AM, Minsky BD, and Guillem J. Male and female sexual and urinary function after total mesorectal excision with autonomic nerve preservation for carcinoma of the rectum. J Am Coll Surg 1996; 182:495-502.

Hays RD, Sherbourne CD, and Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ 1993; 2:217-227.

Heald RJ, Husband EM, and Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg 1982; 69:613-616.

Heald RJ, and Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986; 1:1479-1482.

Hendren SK, O'Connor BI, Liu M, Asano T, Cohen Z, Swallow CJ, Macrae HM, Gryfe R, and McLeod RS. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. Ann Surg 2005; 242:212-223.

Hershman D, Hall MJ, Wang X, Jacobson JS, McBride R, Grann VR, and Neugut AI. Timing of adjuvant chemotherapy initiation after surgery for stage III colon cancer. Cancer 2006; 107:2581-2588.

Hewitson P, Glasziou P, Irwig L, Towler B, and Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev 2007; CD001216.

Hohenberger W, Reingruber B, and Merkel S. Surgery for colon cancer. Scand J Surg 2003; 92:45-52.

Holm T, Ljung A, Haggmark T, Jurell G, and Lagergren J. Extended abdominoperineal resection with gluteus maximus flap reconstruction of the pelvic floor for rectal cancer. Br J Surg 2007; 94:232-238.

Holzer B, Matzel K, Schiedeck T, Christiansen J, Christensen P, Rius J, Richter P, Lehur PA, Masin A, Kuzu MA, Hussein A, Oresland T, Roche B, and Rosen HR. Do geographic and educational factors influence the quality of life in rectal cancer patients with a permanent colostomy? Dis Colon Rectum 2005; 48:2209-2216.

Holzheimer RG. Laparoscopic procedures as a risk factor of deep venous thrombosis, superficial ascending thrombophlebitis and pulmonary embolism--case report and review of the literature. Eur J Med Res 2004; 9:417-422.

Hotta T, Takifuji K, Yokoyama S, Matsuda K, Higashiguchi T, Tominaga T, Oku Y, Nasu T, and Yamaue H. Rectal cancer surgery in the elderly: analysis of consecutive 158 patients with stage III rectal cancer. Langenbecks Arch Surg 2007; 392:549-558.

Huhtinen H, and Rantala A. Surgical treatment of colon cancer. Suomen lääkärilehti 2006; 61:173-176.

Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, and Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350:2335-2342.

Höckerstedt K, Färkkilä M, Kivilaakso E, and Pikkarainen P, 2000, Gastroenterilogia, Duodecim.

Jayne DG, Brown JM, Thorpe H, Walker J, Quirke P, and Guillou PJ. Bladder and sexual function following resection for rectal cancer in a randomized clinical trial of laparoscopic versus open technique. Br J Surg 2005; 92:1124-1132.

Jess P, Christiansen J, and Bech P. Quality of life after anterior resection versus abdominoperineal extirpation for rectal cancer. Scand J Gastroenterol 2002; 37:1201-1204.

Jestin P, Pahlman L, and Gunnarsson U. Risk factors for anastomotic leakage after rectal cancer surgery: a case-control study. Colorectal Dis 2008; 10:715-721.

Joffe J, and Gordon PH. Palliative resection for colorectal carcinoma. Dis Colon Rectum 1981; 24:355-360.

Järvinen HJ. Hereditary cancer: guidelines in clinical practice. Colorectal cancer genetics. Ann Oncol 2004; 15 127-131.

Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, and van de Velde CJ. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001; 345:638-646.

Karanjia ND, Schache DJ, North WR, and Heald RJ. 'Close shave' in anterior resection. Br J Surg 1990; 77:510-512.

Keighley MR, and Matheson D. Functional results of rectal excision and endo-anal anastomosis. Br J Surg 1980; 67:757-761.

Kellokumpu IH, and Mecklin JP. Rectal cancer. Duodecim 2002; 8:797-804.

Kiran RP, Pokala N, and Dudrick SJ. Long-term outcome after operative intervention for rectal cancer in patients aged over 80 years: analysis of 9,501 patients. Dis Colon Rectum 2007; 50:604-610.

Klessen C, Rogalla P, and Taupitz M. Local staging of rectal cancer: the current role of MRI. Eur Radiol 2007; 17:379-389.

Kosmider S, and Lipton L. Adjuvant therapies for colorectal cancer. World J Gastroenterol 2007; 13:3799-3805.

Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, Kubista TP, Poon MA, Meyers WC, Mailliard JA, and et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991; 324:709-715.

Kuvshinoff B, Maghfoor I, Miedema B, Bryer M, Westgate S, Wilkes J, and Ota D. Distal margin requirements after preoperative chemoradiotherapy for distal rectal carcinomas: are < or = 1 cm distal margins sufficient? Ann Surg Oncol 2001; 8:163-169.

Kuzu MA, Topcu O, Ucar K, Ulukent S, Unal E, Erverdi N, Elhan A, and Demirci S. Effect of sphincter-sacrificing surgery for rectal carcinoma on quality of life in Muslim patients. Dis Colon Rectum 2002; 45:1359-1366.

Kyllönen LE. Obstruction and perforation complicating colorectal carcinoma. An epidemiologic and clinical study with special reference to incidence and survival. Acta Chir Scand 1987; 153:607-614.

Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, and Visa J. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002; 359:2224-2229.

Lange MM, Maas CP, Marijnen CA, Wiggers T, Rutten HJ, Kranenbarg EK, and van de Velde CJ. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. Br J Surg 2008; 95:1020-1028.

Latkauskas T, Paskauskas S, Dambrauskas Z, Gudaityte J, Saladzinskas S, Tamelis A, and Pavalkis D. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer: a meta-analysis. Colorectal Dis; doi: 10.1111/j.1463-1318.2009.02015.

Law WL, Choi HK, Ho JW, Lee YM, and Seto CL. Outcomes of surgery for mid and distal rectal cancer in the elderly. World J Surg 2006; 30:598-604.

Law WL, Choi HK, Lee YM, and Chu KW. Palliation for advanced malignant colorectal obstruction by self-expanding metallic stents: prospective evaluation of outcomes. Dis Colon Rectum 2004; 47:39-43.

Law WL, and Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg 2004; 240:260-268.

Lazorthes F, Fages P, Chiotasso P, Lemozy J, and Bloom E. Resection of the rectum with construction of a colonic reservoir and colo-anal anastomosis for carcinoma of the rectum. Br J Surg 1986; 73:136-138.

Le AT, Albo D, and Berger DH. Quality of life in the elderly with rectal cancer. J Am Coll Surg 2007; 205:124-131.

Lee AY, and Levine MN. Venous thromboembolism and cancer: risks and outcomes. Circulation 2003; 107:I17-21.

Lee SH, Hernandez de Anda E, Finne CO, Madoff RD, and Garcia-Aguilar J. The effect of circumferential tumor location in clinical outcomes of rectal cancer patients treated with total mesorectal excision. Dis Colon Rectum 2005; 48:2249-2257.

Lee SJ, and Park YS. Serial evaluation of anorectal function following low anterior resection of the rectum. Int J Colorectal Dis 1998; 13:241-246.

Leo E, Belli F, Miceli R, Mariani L, Gallino G, Battaglia L, Vannelli A, and Andreola S. Distal clearance margin of 1 cm or less: a safe distance in lower rectum cancer surgery. Int J Colorectal Dis 2008; 24:317-322.

Leonardi MJ, McGory ML, and Ko CY. A systematic review of deep venous thrombosis prophylaxis in cancer patients: implications for improving quality. Ann Surg Oncol 2007; 14:929-936.

Leung KL, Kwok SP, Lam SC, Lee JF, Yiu RY, Ng SS, Lai PB, and Lau WY. Laparoscopic resection of rectosigmoid carcinoma: prospective randomised trial. Lancet 2004; 363:1187-1192.

Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, Dash C, Giardiello FM, Glick S, Levin TR, Pickhardt P, Rex DK, Thorson A, and Winawer SJ. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008; 58:130-160.

Liu SK, Church JM, Lavery IC, and Fazio VW. Operation in patients with incurable colon cancer-is it worthwhile? Dis Colon Rectum 1997; 40:11-14.

Lonner JH, Frank J, McGuire K, and Lotke PA. Postthrombotic syndrome after asymptomatic deep vein thrombosis following total knee and hip arthroplasty. Am J Orthop 2006; 35:469-472.

Lundby L, Krogh K, Jensen VJ, Gandrup P, Qvist N, Overgaard J, and Laurberg S. Long-term anorectal dysfunction after postoperative radiotherapy for rectal cancer. Dis Colon Rectum 2005; 48:1343-1349;

Maas CP, Moriya Y, Steup WH, Klein Kranenbarg E, and van de Velde CJ. A prospective study on radical and nerve-preserving surgery for rectal cancer in the Netherlands. Eur J Surg Oncol 2000; 26:751-757.

Macdonald JS. Adjuvant therapy of colon cancer. CA Cancer J Clin 1999; 49:202-219.

Machado M, Nygren J, Goldman S, and Ljungqvist O. Similar outcome after colonic pouch and side-to-end anastomosis in low anterior resection for rectal cancer: a prospective randomized trial. Ann Surg 2003; 238:214-220.

Marks JH, Kawun UB, Hamdan W, and Marks G. Redefining contraindications to laparoscopic colorectal resection for high-risk patients. Surg Endosc 2008; 22:1899-1904.

Marr R, Birbeck K, Garvican J, Macklin CP, Tiffin NJ, Parsons WJ, Dixon MF, Mapstone NP, Sebag-Montefiore D, Scott N, Johnston D, Sagar P, Finan P, and Quirke P. The modern abdominoperineal excision: the next challenge after total mesorectal excision. Ann Surg 2005; 242:74-82.

Martijn H, and Vulto JC. Should radiotherapy be avoided or delivered differently in elderly patients with rectal cancer? Eur J Cancer 2007; 43:2301-2306.

McArdle CS, McMillan DC, and Hole DJ. The impact of blood loss, obstruction and perforation on survival in patients undergoing curative resection for colon cancer. Br J Surg 2006; 93:483-488.

Mecklin JP. The implications of genetics in colorectal cancer. Ann Oncol 2008; 19 Suppl 5:v87-90.

Meyerhardt JA, Tepper JE, Niedzwiecki D, Hollis DR, Schrag D, Ayanian JZ, O'Connell MJ, Weeks JC, Mayer RJ, Willett CG, MacDonald JS, Benson AB, 3rd, and Fuchs CS. Impact of hospital procedure volume on surgical operation and long-term outcomes in high-risk curatively resected rectal cancer: findings from the Intergroup 0114 Study. J Clin Oncol 2004; 22:166-174.

Millikan KW, Staren ED, and Doolas A. Invasive therapy of metastatic colorectal cancer to the liver. Surg Clin North Am 1997; 77:27-48.

Mismetti P, Laporte S, Darmon JY, Buchmuller A, and Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg 2001; 88:913-930.

Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, Ungerleider JS, Emerson WA, Tormey DC, Glick JH, and et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990; 322:352-358.

Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen CM, Ungerleider JS, Emerson WA, Tormey DC, Glick JH, Veeder MH, and Mailliard JA. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann Intern Med 1995; 122:321-326.

Moriya Y. Function preservation in rectal cancer surgery. Int J Clin Oncol 2006; 11:339-343.

Murata A, Brown CJ, Raval M, and Phang PT. Impact of short-course radiotherapy and low anterior resection on quality of life and bowel function in primary rectal cancer. Am J Surg 2008; 195:611-615.

Muthusamy VR, and Chang KJ. Optimal methods for staging rectal cancer. Clin Cancer Res 2007; 13:6877-6884.

Mäkinen MJ. Colorectal serrated adenocarcinoma. Histopathology 2007; 50:131-150.

Nagtegaal ID, van de Velde CJ, Marijnen CA, van Krieken JH, and Quirke P. Low rectal cancer: a call for a change of approach in abdominoperineal resection. J Clin Oncol 2005; 23:9257-9264.

Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, Miedema B, Ota D, and Sargent D. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001; 93:583-596.

Nesbakken A, Nygaard K, Bull-Njaa T, Carlsen E, and Eri LM. Bladder and sexual dysfunction after mesorectal excision for rectal cancer. Br J Surg 2000; 87:206-210.

Nesbakken A, Nygaard K, Westerheim O, Lunde OC, and Mala T. Audit of intraoperative and early postoperative complications after introduction of mesorectal excision for rectal cancer. Eur J Surg 2002; 168:229-235.

Nordic Gastrointestinal Tumor Adjuvant Therapy Group. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. J Clin Oncol 1992; 10:904-911.

Odonnell M, and Kearon C. Thromboembolism prevention in ischaemic stroke. Lancet 2007; 369:1413-1415.

Ortiz H, and Armendariz P. Anterior resection: do the patients perceive any clinical benefit? Int J Colorectal Dis 1996; 11:191-195.

Ota DM, Jacobs L, and Kuvshinoff B. Rectal cancer: the sphincter-sparing approach. Surg Clin North Am 2002; 82:983-993.

Parkin DM, Bray F, Ferlay J, and Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55:74-108.

Peeters KC, Kapiteijn E, and van de Velde CJ. Managing rectal cancer: the Dutch experience. Colorectal Dis 2003; 5:423-426.

Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, Rutten H, Pahlman L, Glimelius B, Leer JW, and van de Velde CJ. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007; 246:693-701.

Penopoulos V, Handolias M, Avgerinos A, Maris T, Ilias T, Issopoulos N, Christianopoulos G, Betsis D, Vrettou E, Kitis G, and Pistevou K. A short course of preoperative radiotherapy improves prognosis of operable rectal carcinoma: a case control study. Hepatogastroenterology 2008; 55:1280-1287.

Pesavento R, Bernardi E, Concolato A, Dalla Valle F, Pagnan A, and Prandoni P. Postthrombotic syndrome. Semin Thromb Hemost 2006; 32:744-751.

Petrelli N, Rosenfield L, Herrera L, and Mittelman A. The morbidity of perineal wounds following abdominoperineal resection for rectal carcinoma. J Surg Oncol 1986; 32:138-140.

Pietrzak L, Bujko K, Nowacki MP, Kepka L, Oledzki J, Rutkowski A, Szmeja J, Kladny J, Dymecki D, Wieczorek A, Pawlak M, Lesniak T, Kowalska T, and Richter P. Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: report of a randomised trial. Radiother Oncol 2007; 84:217-225.

Pietsch AP, Fietkau R, Klautke G, Foitzik T, and Klar E. Effect of neoadjuvant chemoradiation on postoperative fecal continence and anal sphincter function in rectal cancer patients. Int J Colorectal Dis 2007; 22:1311-1317.

Pollack J, Holm T, Cedermark B, Altman D, Holmstrom B, Glimelius B, and Mellgren A. Late adverse effects of short-course preoperative radiotherapy in rectal cancer. Br J Surg 2006; 93:1519-1525.

Ptok H, Meyer F, Marusch F, Steinert R, Gastinger I, Lippert H, and Meyer L. Palliative stent implantation in the treatment of malignant colorectal obstruction. Surg Endosc 2006; 20:909-914.

Puig-La Calle J, Jr., Quayle J, Thaler HT, Shi W, Paty PB, Quan SH, Cohen AM, and Guillem JG. Favorable short-term and long-term outcome after elective radical rectal cancer resection in patients 75 years of age or older. Dis Colon Rectum 2000; 43:1704-1709.

Rasmussen OO, Petersen IK, and Christiansen J. Anorectal function following low anterior resection. Colorectal Dis 2003; 5:258-261.

Rauch P, Miny J, Conroy T, Neyton L, and Guillemin F. Quality of life among disease-free survivors of rectal cancer. J Clin Oncol 2004; 22:354-360.

Renehan AG, Egger M, Saunders MP, and O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. BMJ 2002; 324:813.

Repici A, Fregonese D, Costamagna G, Dumas R, Kahler G, Meisner S, Giovannini M, Freeman J, Petruziello L, Hervoso C, Comunale S, and Faroux R. Ultraflex precision colonic stent placement for palliation of malignant colonic obstruction: a prospective multicenter study. Gastrointest Endosc 2007; 66:920-927.

Repici A, Reggio D, De Angelis C, Barletti C, Marchesa P, Musso A, Carucci P, Debernardi W, Falco M, Rizzetto M, and Saracco G. Covered metal stents for management of inoperable malignant colorectal strictures. Gastrointest Endosc 2000; 52:735-740.

Ristamäki R, Österlund P, and Pyrhönen S. Treatment of metastatic colorectal cancer. Suomen Lääkärilehti 2006; 61:189-193.

Rockey DC, Paulson E, Niedzwiecki D, Davis W, Bosworth HB, Sanders L, Yee J, Henderson J, Hatten P, Burdick S, Sanyal A, Rubin DT, Sterling M, Akerkar G, Bhutani MS, Binmoeller K, Garvie J, Bini EJ, McQuaid K, Foster WL, Thompson WM, Dachman A, and Halvorsen R. Analysis of air contrast barium enema, computed tomographic

colonography, and colonoscopy: prospective comparison. Lancet 2005; 365:305-311.

Rullier E, Laurent C, Bretagnol F, Rullier A, Vendrely V, and Zerbib F. Sphincter-saving resection for all rectal carcinomas: the end of the 2-cm distal rule. Ann Surg 2005; 241:465-469.

Rullier E, Sa Cunha A, Couderc P, Rullier A, Gontier R, and Saric J. Laparoscopic intersphincteric resection with coloplasty and coloanal anastomosis for mid and low rectal cancer. Br J Surg 2003; 90:445-451.

Saclarides TJ. Transanal endoscopic microsurgery. Surg Clin North Am 1997; 77:229-239.

Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, and Raab R. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004; 351:1731-1740.

Schmidt CE, Bestmann B, Kuchler T, Longo WE, and Kremer B. Prospective evaluation of quality of life of patients receiving either abdominoperineal resection or sphincter-preserving procedure for rectal cancer. Ann Surg Oncol 2005a; 12:117-123.

Schmidt CE, Bestmann B, Kuchler T, Longo WE, and Kremer B. Ten-year historic cohort of quality of life and sexuality in patients with rectal cancer. Dis Colon Rectum 2005b; 48:483-492.

Sebastian S, Johnston S, Geoghegan T, Torreggiani W, and Buckley M. Pooled analysis of the efficacy and safety of self-expanding metal stenting in malignant colorectal obstruction. Am J Gastroenterol 2004; 99:2051-2057.

Sengupta S, and Tjandra JJ. Local excision of rectal cancer: what is the evidence? Dis Colon Rectum 2001; 44:1345-1361.

Stipa F, Pigazzi A, Bascone B, Cimitan A, Villotti G, Burza A, and Vitale A. Management of obstructive colorectal cancer with endoscopic stenting followed by single-stage surgery: open or laparoscopic resection? Surg Endosc 2008; 22:1477-1481

Strohlein MA, Grutzner KU, Jauch KW, and Heiss MM. Comparison of laparoscopic vs. open access surgery in patients with rectal cancer: a prospective analysis. Dis Colon Rectum 2008; 51:385-391.

Sugarbaker PH, and Corlew S. Influence of surgical techniques on survival in patients with colorectal cancer. Dis Colon Rectum 1982; 25:545-557.

Suzuki N, Saunders BP, Thomas-Gibson S, Akle C, Marshall M, and Halligan S. Colorectal stenting for malignant and benign disease: outcomes in colorectal stenting. Dis Colon Rectum 2004; 47:1201-1207.

Swanson RS, Compton CC, Stewart AK, and Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 2003; 10:65-71.

Tan WS, Tang CL, Shi L, and Eu KW. Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. Br J Surg 2009; 96:462-472.

Tilney HS, and Tekkis PP. Extending the horizons of restorative rectal surgery: intersphincteric resection for low rectal cancer. Colorectal Dis 2008; 10:3-15.

Tjandra JJ, Kilkenny JW, Buie WD, Hyman N, Simmang C, Anthony T, Orsay C, Church J, Otchy D, Cohen J, Place R, Denstman F, Rakinic J, Moore R, and Whiteford M. Practice parameters for the management of rectal cancer (revised). Dis Colon Rectum 2005; 48:411-423.

Tomita R, and Igarashi S. A pathophysiological study using anorectal manometry on patients with or without soiling 5 years or more after low anterior resection for lower rectal cancer. Hepatogastroenterology 2008; 55:1584-1588.

Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, Mineur L, Carola E, Etienne PL, Rivera F, Chirivella I, Perez-Staub N, Louvet C, Andre T, Tabah-Fisch I, and de Gramont A. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer--a GERCOR study. J Clin Oncol 2006; 24:394-400.

Turnbull RB, Jr., Kyle K, Watson FR, and Spratt J. Cancer of the colon: the influence of the no-touch isolation technic on survival rates. Ann Surg 1967; 166:420-427.

Ulrich A, Z'Graggen K, Schmitz-Winnenthal H, Weitz J, and Buchler MW. The transverse coloplasty pouch. Langenbecks Arch Surg 2005; 390:355-360.

Valero G, Lujan JA, Hernandez Q, De Las Heras M, Pellicer E, Serrano A, and Parrilla P. Neoadjuvant radiation and chemotherapy in rectal cancer does not increase postoperative complications. Int J Colorectal Dis 2003; 18:495-499.

Van Cutsem E, Dicato M, Haustermans K, Arber N, Bosset JF, Cunningham D, De Gramont A, Diaz-Rubio E, Ducreux M, Goldberg R, Glynne-Jones R, Haller D, Kang YK, Kerr D, Labianca R, Minsky BD, Moore M, Nordlinger B, Rougier P, Scheithauer W, Schmoll HJ, Sobrero A, Tabernero J, Tempero M, Van de Velde C, and Zalcberg J. The diagnosis and management of rectal cancer: expert discussion and recommendations derived from the 9th World Congress on Gastrointestinal Cancer, Barcelona, 2007. Ann Oncol 2008; 19 Suppl 6:vi1-8.

Van Cutsem E, Dicato M, Wils J, Cunningham D, Diaz-Rubio E, Glimelius B, Haller D, Johnston P, Kerr D, Koehne CH, Labianca R, Minsky B, Nordlinger B, Roth A, Rougier P, and Schmoll HJ. Adjuvant treatment of colorectal cancer (current expert opinion derived from the Third International Conference: Perspectives in Colorectal Cancer, Dublin, 2001). Eur J Cancer 2002; 38:1429-1436.

van Hooft JE, Fockens P, Marinelli AW, Timmer R, van Berkel AM, Bossuyt PM, and Bemelman WA. Early closure of a multicenter randomized clinical trial of endoscopic stenting versus surgery for stage IV left-sided colorectal cancer. Endoscopy 2008; 40:184-191.

Wang C, Zhou ZG, Yu YY, Shu Y, Li Y, Yang L, and Li L. Occurrence and prognostic value of circumferential resection margin involvement for patients with rectal cancer. Int J Colorectal Dis 2009; 24:385-390.

Ware JE, Jr., Kosinski M, Gandek B, Aaronson NK, Apolone G, Bech P, Brazier J, Bullinger M, Kaasa S, Leplege A, Prieto L, and Sullivan M. The factor structure of the SF-36 Health Survey in 10 countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol 1998; 51:1159-1165.

Watt AM, Faragher IG, Griffin TT, Rieger NA, and Maddern GJ. Self-expanding metallic stents for relieving malignant colorectal obstruction: a systematic review. Ann Surg 2007; 246:24-30.

Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Pahlman L,

Cuesta MA, Msika S, Morino M, and Lacy AM. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005; 6:477-484.

Wiggers T, Arends JW, and Volovics A. Regression analysis of prognostic factors in colorectal cancer after curative resections. Dis Colon Rectum 1988a; 31:33-41.

Wiggers T, Jeekel J, Arends JW, Brinkhorst AP, Kluck HM, Luyk CI, Munting JD, Povel JA, Rutten AP, Volovics A, and et al. No-touch isolation technique in colon cancer: a controlled prospective trial. Br J Surg 1988b; 75:409-415.

Willis S, Kasperk R, Braun J, and Schumpelick V. Comparison of colonic J-pouch reconstruction and straight coloanal anastomosis after intersphincteric rectal resection. Langenbecks Arch Surg 2001; 386:193-199.

Vironen JH, Kairaluoma M, Aalto AM, and Kellokumpu IH. Impact of functional results on quality of life after rectal cancer surgery. Dis Colon Rectum 2006; 49:568-578.

Vironen JH, Sainio P, Husa AI, and Kellokumpu IH. Complications and survival after surgery for rectal cancer in patients younger than and aged 75 years or older. Dis Colon Rectum 2004; 47:1225-1231.

Wolmark N, Yothers G, O'Connell MJ, Sharif S, Atkins JN, Seay TE, Feherenbacher L, O'Reilly S, and Allegra CJ. A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: Results of NSABP Protocol C-08. Journal of Clinical Oncology 2009; 27:ASCO Annual Meeting Proceedings (Post-Meeting Edition).

Wolpin BM, Meyerhardt JA, Mamon HJ, and Mayer RJ. Adjuvant treatment of colorectal cancer. CA Cancer J Clin 2007; 57:168-185.

Yang L, Yu YY, Zhou ZG, Li Y, Xu B, Song JM, Liu HY, and Jiang X. Quality of life outcomes following laparoscopic total mesorectal excision for low rectal cancers: a clinical control study. Eur J Surg Oncol 2007; 33:575-579.

Yun HR, Lee LJ, Park JH, Cho YK, Cho YB, Lee WY, Kim HC, Chun HK, and Yun SH. Local recurrence after curative resection in patients with colon and rectal cancers. Int J Colorectal Dis 2008; 23:1081-1087.