SURGICAL TREATMENT OF COLORECTAL CANCER – CONTROVERSIAL ISSUES

by

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ABSTRACT

Pirita Varpe

Surgical treatment of colorectal cancer – controversial issues
From the Department of Surgery, University of Turku, Turku, Finland.

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

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


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

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


II Varpe P, Huhtinen H, Rantala A, Grönroos J. Thromboprophylaxis following surgery for colorectal cancer - is it worthwhile after hospital discharge?

Aging Clin Exp Res, in press

Colorectal Dis, in press

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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.
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 (Table 1) 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.

<table>
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<tr>
<th>stage</th>
<th>TNM*</th>
<th>Modified Dukes*</th>
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<tr>
<td>I</td>
<td>T1-2 N0 M0</td>
<td>A</td>
</tr>
<tr>
<td>II A</td>
<td>T3 N0 M0</td>
<td>B</td>
</tr>
<tr>
<td>II B</td>
<td>T4 N0 M0</td>
<td>B</td>
</tr>
<tr>
<td>III A</td>
<td>T1-2 N1 M0</td>
<td>C</td>
</tr>
<tr>
<td>III B</td>
<td>T3-4 N1 M0</td>
<td>C</td>
</tr>
<tr>
<td>III C</td>
<td>any T N2 M0</td>
<td>C</td>
</tr>
<tr>
<td>IV</td>
<td>any T any N M1</td>
<td>D</td>
</tr>
</tbody>
</table>

*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 hemicolecctomy, transverse colectomy, a left hemicolecctomy or sigmoid resection. These operations are shown in Figure 2.

![Figure 2](image)

**Figure 2.** The surgical treatment of CRC depending on the location of the tumour a) right hemicolecctomy b) transverse colectomy c) left hemicolecctomy 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).
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
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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 tumor stage, 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).
Figure 4. The pelvic autonomic nerve system. The sympathetic 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 parasympathetic 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 (Table 1) 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...
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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).

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>5-year survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-2N0M0</td>
<td>85-95</td>
</tr>
<tr>
<td>T3-4N0M0</td>
<td>60-80</td>
</tr>
<tr>
<td>T1-4N1-2M0</td>
<td>30-60</td>
</tr>
<tr>
<td>T1-4N0-2M1</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>surgical procedure</th>
<th>number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ileocecal resection</td>
<td>5</td>
</tr>
<tr>
<td>right hemicolecotmy</td>
<td>111</td>
</tr>
<tr>
<td>resection of transverse colon</td>
<td>7</td>
</tr>
<tr>
<td>left hemicolecotmy</td>
<td>19</td>
</tr>
<tr>
<td>sigmoid resection</td>
<td></td>
</tr>
<tr>
<td>other resection of colon</td>
<td>12</td>
</tr>
<tr>
<td>Hartman procedure</td>
<td>15</td>
</tr>
<tr>
<td>anterior resection</td>
<td>125</td>
</tr>
<tr>
<td>abdominoperineal resection</td>
<td>58</td>
</tr>
<tr>
<td>subtotal colectomy</td>
<td>8</td>
</tr>
<tr>
<td>reversal of Hartman procedure</td>
<td>2</td>
</tr>
<tr>
<td>laparotomy and sigmoidostomy</td>
<td>2</td>
</tr>
<tr>
<td>ileotransversostomy</td>
<td>10</td>
</tr>
<tr>
<td>gastrojejunostomy</td>
<td>4</td>
</tr>
<tr>
<td>resection of small intestine</td>
<td>3</td>
</tr>
<tr>
<td>explorative laparotomy</td>
<td>35</td>
</tr>
</tbody>
</table>

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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).

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

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
Patients and Methods

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).

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

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.
### Patients and Methods

**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™ 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 recurrences of successfully inserted stents.
Table 6. Details of patients with malignant colorectal obstruction and results of insertion of SEMS.

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

UP= Ultraflex Precision™, H = Hanarostent™, += yes, -= no

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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.

<table>
<thead>
<tr>
<th>patient number</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years)</td>
<td>92</td>
<td>68</td>
<td>80</td>
</tr>
<tr>
<td>tumour site</td>
<td>caecum</td>
<td>ascending colon</td>
<td>rectum</td>
</tr>
<tr>
<td>tumour stage</td>
<td>T3N0M0</td>
<td>T3N1M0</td>
<td>M1</td>
</tr>
<tr>
<td>operation</td>
<td>JFB30</td>
<td>JFB30</td>
<td>JFF26</td>
</tr>
<tr>
<td>duration of prophylaxis (days)</td>
<td>13</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>event</td>
<td>PE</td>
<td>DVT</td>
<td>DVT</td>
</tr>
<tr>
<td>occurred on postoperative day</td>
<td>16</td>
<td>78</td>
<td>63</td>
</tr>
</tbody>
</table>

JFB30= right hemicolectomy, JFF26= laparotomy and sigmoidostomy
PE =pulmonary embolism, DVT= deep venous thrombosis

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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.

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

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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
Discussion

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% to 1.6% (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™ 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 should 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.
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Pirita Varpe
REFERENCES


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


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.
References


References


References


References


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.


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.


