COLON CANCER
Management and outcome in a Swedish population

Annika Sjövall

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Department of Surgery, Karolinska University Hospital
Department of Molecular Medicine and Surgery, Karolinska Institutet
Stockholm, Sweden
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“Det är inte alltid tillräckligt att förstå ett problem för att lösa det – men det är alltid nödvändigt”

Göran Rosenberg, DN Opinion 10 okt 2006
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Papers I-IV
Colon cancer is common in Sweden, with about 3500 new cases every year. Tumours of the colon and rectum are usually addressed as an entity. Great effort has been made to improve the outcome after rectal cancer treatment with subsequent improvement of survival. Only few studies have addressed the specific issue of colon cancer and how to improve the outcome for this large group of patients. As a consequence, the 5-year survival after colon cancer treatment in Sweden is now poorer than after rectal cancer treatment. 

Since 1996, the Stockholm-Gotland region has a common management protocol for patients with colon cancer. As part of this protocol, data on all patients with newly diagnosed colon cancer in the region are prospectively collected in a database at the Oncologic Centre in Stockholm. The database includes information on age, sex, tumour location and stage, emergency or elective surgery, type of surgery performed, postoperative mortality, histopathology of the tumour and follow-up data on recurrence and survival. The database is continuously validated and updated through comparison to other registers with information on healthcare consumption, diagnoses according to the international classification of diseases (ICD) and causes of death.

This thesis is based on information from the Oncologic Centre database and includes all patients diagnosed with colon cancer in the Stockholm-Gotland region during 1996-2000, followed until January 2005. The aim of the thesis was to achieve knowledge on how patients with colon cancer have been managed in the region during these years and to assess the outcome in terms of postoperative mortality, loco-regional and distant recurrence and survival. Another aim was to identify risk factors for death and recurrence.

During the study period, 2855 patients were diagnosed with colon cancer. After the exclusion of 80 patients diagnosed at autopsy, 2775 were eligible for follow-up. The crude 5-year survival for all patients was 46 per cent. Nine hospitals managed these patients, and differences in overall survival and risk for local recurrence between the hospitals were present despite the common management protocol. The cumulative risk for loco-regional recurrence was 11 per cent. Tumour location in the right flexure and sigmoid colon, more advanced T-stage and N-stage, bowel perforation, emergent surgery and poor tumour differentiation were identified as risk factors for loco-regional recurrence. After complete resection of loco-regional recurrences, the estimated 5-year survival was 43 per cent, while there were no 5-year survivors among patients where a complete resection of the recurrence could not be accomplished.

Liver metastases were detected in 24 per cent of the patients during follow-up. The hepatic resection rate was four per cent, which is remarkably low. A retrospective evaluation of radiological images of the liver showed that ten per cent of the patients might have been candidates for liver surgery. An evaluation of tumour volume as a prognostic factor showed that an increased tumour volume was associated with poorer survival even after adjusting for other postoperatively known factors. Some areas of possible improvement were identified. A multidisciplinary approach to improve preoperative staging, surgery, histopathologic staging and selection of patients for medical oncologic treatment could probably improve the outcome for patients with colon cancer.
LIST OF ABBREVIATIONS

AJCC          The American Joint Commission of Cancer
BMI           Body mass index
CEA           Carcinoembryonic antigen
CI            Confidence interval
CT            Computed tomography
DW-MRI        Diffusion-weighted magnetic resonance imaging
ERAS          Enhanced recovery after surgery
HR            Hazard ratio
IM            Index of metastases
FAP           Familial adenomatous polyposis
5-FU          5-Fluorouracil
HNPCC         Hereditary non-polyposis colorectal cancer
ICD           International Classification of Diseases
MRI           Magnetic resonance imaging
NSAID         Nonsteroidal anti-inflammatory drug
PCR           Polymerase chain reaction
PET           Positron emission tomography
SCCSG         Stockholm Colorectal Cancer Study Group
SN            Sentinel node
TME           Total mesorectal excision
TNM           Tumour Node Metastasis
UICC          Union Internationale Contre le Cancer
List of Publications

This thesis is based on the following papers, which will be referred to by their Roman numerals (I-IV):

I. Colon cancer management and outcome in relation to individual hospitals in a defined population.
Sjövall A, Holm T, Singnomklao T, Granath F, Glimelius B, Cedermark B
*British Journal of Surgery, in press*
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II. Loco-regional Recurrence from Colon Cancer: A Population-based Study.
Sjövall A, Granath F, Cedermark B, Glimelius B, Holm T
*Annals of Surgical Oncology, in press. Published online 1 December 2006* With kind permission of Springer Science and Business Media.

III. The potential for improved outcome in patients with hepatic metastases from colon cancer: a population-based study.
Sjövall A, Järv V, Blomqvist L, Singnomklao T, Cedermark B, Glimelius B, Holm T
*European Journal of Surgical Oncology, 2004 Oct; 30 (8): 834-41* With kind permission from Elsevier

IV. Tumor volume as a prognostic factor in colon cancer.
Sjövall A, Hellborg H, Cedermark B, Glimelius B, Holm T
Submitted
## Thesis at a glance

<table>
<thead>
<tr>
<th>Question</th>
<th>Patients and methods</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I</strong> What is the outcome of management of colon cancer in the Stockholm-Gotland region and are there differences between hospitals?</td>
<td>All 2855 patients diagnosed with colon cancer in the region during 1996-2000, followed until Jan 2005</td>
<td>Crude 5-year survival for all patients was 46%. The individual hospital was an independent risk factor for death.</td>
<td>There are differences in survival rates between hospitals despite a common management protocol. Measures to improve management need to be undertaken.</td>
</tr>
<tr>
<td><strong>II</strong> How frequent are loco-regional recurrences from colon cancer in the Stockholm-Gotland region, how are they treated, what is the outcome and what risk factors can be identified?</td>
<td>All 1856 patients with colon cancer operated on with potentially curative surgery in the region during 1996-2000, and surviving more than 30 days postoperatively, followed until Jan 2005</td>
<td>The cumulative 5-year incidence was 11%. The median survival was 9 months. Surgery was performed in 57% of the cases. Tumour location, emergent surgery, bowel perforation, TN-stage and tumour differentiation were independent risk factors for loco-regional recurrence.</td>
<td>Loco-regional recurrence from colon cancer is a significant clinical problem and multidisciplinary treatment programmes seem crucial to improve outcome.</td>
</tr>
<tr>
<td><strong>III</strong> How have liver metastases from colon cancer been treated in the Stockholm-Gotland region, what is the outcome and would more patients have been suited for liver surgery?</td>
<td>All 2280 patients diagnosed with colon cancer in the region during 1996-1999, followed until Jan 2003. All CT/MRI of the liver were re-evaluated.</td>
<td>508 patients with liver metastases were followed. 21 (4%) had hepatic resection, 8 had no evidence of disease at the end of follow-up. Re-evaluation of CT/MRI showed that 50 patients might have been candidates for primary liver surgery.</td>
<td>The hepatic resection rate was low. There is a potential for an increased resection rate with dedicated multidisciplinary management programmes.</td>
</tr>
<tr>
<td><strong>IV</strong> Is tumour volume a prognostic factor in colon cancer?</td>
<td>All 1865 patients diagnosed with colon cancer in the Stockholm-Gotland region during 1996-2000 and with tumour size in three dimensions recorded.</td>
<td>A small tumour volume correlated with good outcome and a large volume with poor outcome.</td>
<td>Tumour volume may be useful as a preoperative prognostic factor, but further studies are needed for clinical implementation.</td>
</tr>
</tbody>
</table>
In studies of colon cancer, much of the available information considers cancer in the colon and in the rectum as a common entity. This is reasonable, since the colon and the rectum are both part of the large bowel and the diseases share many common features (Fig. 1). Nevertheless, it is important to distinguish between the two, since there are differences in the treatment and outcome.

Many studies have been performed with the specific aim of improving the outcome of treatment for rectal cancer by radiation therapy and by introduction of a precise surgical technique with a thorough dissection in embryological layers \(^1\text{ - }^7\). The treatment of patients with colon cancer has, however, been less scrutinized and thus remained essentially unchanged during the past decades. Historically, the survival after colon cancer has been better than after rectal cancer, but the efforts regarding management of rectal cancer have resulted in better outcome. The survival after colon cancer treatment is no longer better than after rectal cancer treatment in Sweden \(^8\text{, }^9\). Since colon cancer is common in Sweden, with about 3500 new cases every year \(^10\), the time has come to direct specific attention towards management of colon cancer, with the aim of improving the outcome for this large group of patients. This thesis includes only patients with colon cancer and is a part of initiating this process of improvement.

Figure 1. *The anatomy of the gastrointestinal tract.*
Epidemiology
Colon cancer is one of the most common cancers in Western populations\textsuperscript{11-13}. The highest incidence rates are found in Australia, North America and Western Europe, whilst the lowest are found in developing countries, such as India and African countries\textsuperscript{14, 15}. The tumour predominates in populations with high income and high educational levels, and it has been found that it occurs more frequently in urban than in rural areas. Some of the large differences between countries may be due to the failure to detect colon cancer in developing countries, where resources for diagnosis are scarce. This explanation can, however, only account for a small part of the variations. There is a slow gradual increase in colon cancer incidence. This increase is more pronounced in areas formerly at low risk but is also seen in the Nordic countries\textsuperscript{16} (Fig. 2) and could be attributable to a rise in the standard of living, but the exact reasons have not been clarified.

In Sweden, colon cancer is the fourth most common form of cancer in males, after prostate, skin and lung cancer, with an age-standardized incidence rate of 44.8 per 100 000 personyears. In females it is the second most common form of cancer in Sweden after breast cancer, with an incidence rate of 36.0 per 100 000\textsuperscript{11}. Stockholm County and the island of Gotland together have a total of 1.9 million inhabitants. In 2004, the age-standardized incidence rate of colon cancer in the region was 42.9 per 100 000 inhabitants (Fig. 2).

![Figure 2. Age standardized incidence rates for colon cancer in the Stockholm-Gotland region per 100 000 personyears.](image-url)
Aetiology
More than 95 per cent of all colon cancers are adenocarcinomas, emerging from the glandular epithelium of the colon. Studies on colon cancer generally refer only to adenocarcinomas, excluding the few cases of squamous cell carcinomas, carcinoids, lymphomas, malignant melanomas and sarcomas.

Hereditary factors
It is generally accepted that most colon cancers develop from a benign adenoma, via different degrees of dysplasia, into an invasive adenocarcinoma. The transformation from a normal cell into a cancer cell includes several steps of genetic changes. The colonic epithelium is normally an actively proliferating system, but as a result of genetic changes, cells in the epithelium of the colon can begin proliferating in an uninhibited way, developing into a malignant tumour.

The genes suggested in the process of tumorigenesis can be subdivided into oncogenes, tumour suppressor genes and DNA stability genes. Oncogenes promote cell proliferation and a mutation in an oncogene can thus induce uninhibited cellular growth. Tumour suppressor genes down-regulate pathways that stimulate growth. Mutations in such genes can inactivate their function and inactivation of a tumour suppressor gene is involved in familial adenomatous polyposis (FAP). DNA stability genes repair DNA replication errors and when these systems are dysfunctional, mutations can accumulate in the genome. Defective DNA stability genes are seen in hereditary non-polyposis colorectal cancer (HNPCC).

Thus, hereditary factors contribute to the development of colorectal cancer, although the proportion of colorectal cancers attributable to the high-penetrance genetic syndromes, FAP and HNPCC is only about 5 per cent. In a population-based study, the risk for colon cancer was significantly higher among relatives, and several mutations involved in colon cancer development have been identified. The actual familial risk, i.e. patients who have two or more first- or second-degree relatives with colorectal cancer, make up approximately 20 per cent of all patients with colorectal cancer. In a study on heritable and environmental factors on twins, the effects of hereditary factors in colorectal cancer was estimated to be 35 per cent.

Environmental factors
A familial occurrence of cancer may be due to a shared environment rather than genetic reasons. Many lifestyle factors and dietary factors have been suggested to increase the risk of developing colon cancer. A high intake of animal fat, alcohol and tobacco, a high body mass index (BMI) and low physical activity all seem to be associated with an increased risk, but the exact causes have not been clearly established. A high intake of milk, calcium and folate is reported to
be associated with a decreased risk for colon cancer. A popular theory is that dietary fibre reduces the risk for colorectal cancer and this has been suggested by case-control studies. However, a recent Cochrane review could not confirm a reduced incidence of adenomatous polyps or colorectal cancer in patients with a high consumption of dietary fibre. The follow-up time in the studies reviewed was, however, only two to four years. There are some data supporting that aspirin (ASA), Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and hormone replacement therapy by estrogens are associated with a reduction in the risk for colon cancer, but further studies on this are needed.

Studies on migrants support the theory that environmental factors play a major role in the aetiology of colorectal cancer, illustrated by an increase in risk for colorectal cancer for the offspring of migrants from low incidence areas to the USA.

**Diagnosis and preoperative staging**

Several randomised trials have shown a reduced mortality rate in colorectal cancer after screening with faecal occult blood test. Such a screening protocol is still a matter of discussion in Sweden and has not yet been introduced. Problems being discussed are issues of a high rate of false positive tests and allocation of financial resources. Therefore, almost all colon cancers are diagnosed based on symptoms. The symptoms are comprised mainly of abdominal pain, diarrhoea or constipation, blood in the stools or fatigue due to anaemia. In the right colon, the faeces are liquid and can pass through a bowel that is strictureed by a tumour. Right-sided tumours can thus cause a tight stricture before mechanical bowel obstruction occurs. Blood from a tumour in the right colon turns dark during the passage through the large bowel, and the patient detects no visible blood in the stool. It is therefore common that the symptoms from these tumours are comprised of fatigue caused by anaemia due to occult bleeding from the tumour. The more distally in the colon the tumour is located, the more solid are the faeces, with subsequent increased risk for obstruction of faecal passage and symptoms associated with mechanical obstruction, such as abdominal pain, constipation or diarrhoea. A distal location of the tumour also increases the chance of visible red blood in the stools, which catches the patient’s attention. Several studies report that 20-30 per cent of all colon cancers are diagnosed in an emergent setting when a mechanical obstruction or tumour perforation is manifest.

In the elective situation, the diagnosis is established by colonoscopy, barium enema or the newer method of computed tomography colonography. In Sweden, it is generally accepted that a preoperative investigation includes evaluation regarding metastases in the liver and the lungs. The abdomen is examined by computed tomography (CT) or contrast enhanced ultrasonography and the lungs by CT or plain...
X-ray. It has generally not been part of a standard management plan to evaluate the primary tumour regarding the extent of local growth. Such an evaluation could be of value in planning the extent of the resection and to avoid surprises during the operation that might jeopardize a locally complete resection of the tumour. It would be desirable to identify preoperatively measurable prognostic factors to select patients at a high risk of cancer recurrence after surgery. Several tumour markers have been evaluated for this purpose, but the only one that is currently used in clinical practice is carcinoembryonic antigen (CEA)\textsuperscript{48-55}. Tumour size has been evaluated as a variable in several studies on prognostic factors for colorectal cancer, and has been concluded to be inefficient as an independent prognostic factor after adjustment for TNM stage\textsuperscript{56-59}. It has, however, not been established whether tumour volume, which could probably be measured by radiological methods, could be a preoperative prognostic factor that might influence the management and surgery before the T- and N-stages are known.

**Management**

*Preoperative preparation*

In Sweden, routine preoperative preparation since many years consists of antibiotic prophylaxis, prophylaxis against thrombo-embolic complications and mechanical bowel cleansing. There is convincing evidence that antimicrobial prophylaxis is of importance to avoid postoperative infections. It has also been shown that the use of a single dose of an antimicrobial agent is as efficacious as multiple-dose regimens. It seems that the efficiencies of oral and systemic administration are very similar. The exact combination of optimal antibiotic therapy has not been established, since many regimens have similar results. The important principles are that the antibiotics are active against both aerobic and anaerobic bacteria and that they are administered in time, so that the tissue concentration of antibiotics is sufficiently high at the time of surgery\textsuperscript{60, 61}. Colorectal surgery carries a high risk for deep venous thrombosis and pulmonary embolism. It is established that low molecular weight heparin is efficient as prophylaxis and should be used routinely\textsuperscript{62-65}.

Preoperative mechanical bowel preparation has been regarded as an important factor to avoid anastomotic leakage. Since the early 1990s, several randomised trials and meta-analyses have failed to show any advantages of mechanical bowel cleansing versus no bowel preparation\textsuperscript{66, 67}. Bowel preparation is poorly tolerated by the patients, involves an extra burden for the nursing staff and it can be concluded that this regimen has no place in elective open colon surgery. This conclusion is supported by a Swedish randomised controlled trial including 1343 patients, where no differences in the overall complications could be seen between the group that had bowel preparation compared to the one that did not\textsuperscript{68}. 

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Surgical techniques

Surgery with resection of the colon segment containing the tumour and its regional lymph nodes is the first-line treatment for colon cancer. Reybard from Lyon appears to be the first on record to have performed a successful resection of a colon cancer with subsequent anastomosis, in 1833. The problems with intra-abdominal leakage and sepsis were huge and the mortality after resection and anastomosis was still 40 per cent at the end of the nineteenth century. In order to avoid the intra-abdominal anastomoses, Bloch in Copenhagen (1894), Paul of Liverpool (1895) and von Mikulicz of Breslau (1903) independently described similar methods of mobilising and exteriorising the part of the colon with the tumour and thereby leaving the anastomosis extra corporally until it had healed. This method decreased the mortality due to sepsis, but the local recurrence rate was high. The discovery and introduction of antibiotics in the 1940s was a breakthrough in colorectal surgery, reducing mortality due to intra-abdominal sepsis.

Over the past decades, there have been no major changes in the surgical treatment of colon cancer. The surgery includes resection of the colonic segment involved by the tumour and subsequent anastomosis of the bowel to restore continuity. The anastomosis can be handsewn or stapled. Trials comparing these two methods have not shown any significant differences between the two and have concluded that the choice of anastomotic technique should be the surgeon’s preference. A resection of 5-10 centimetres of bowel surrounding the tumour seems to be sufficient for tumour clearance. It is, however, not known how wide the resection of the mesocolon, including blood vessels and lymphatic vessels, should be. Thus, no standard technique for optimal resection of a colon cancer has been clearly established. Lord Moynihan of Leeds stated in 1908 that “The surgery of malignant disease is not the surgery of organs; it is the anatomy of the lymphatic system” and proposed resection of the inferior mesenteric artery at its origin for tumours in the rectum or rectosigmoid. High ligation of vessels has been reported beneficial by other authors but it has not gained total general acceptance. The “no-touch isolation” technique, where the mesenteric vessels are ligated before mobilising the tumour, has been proposed as important to avoid tumour dissemination during surgery but this has not been proven and is currently not part of the standard technique. It is generally accepted that a complete resection of the tumour is the most important factor to reduce the risk for tumour recurrence and a prerequisite for cure. To classify an operation as potentially curative, the resection should be complete according to both the surgeon and the pathologist.
The standard approach for a colon cancer operation is open surgery. The laparoscopic approach has been evaluated in several randomised trials. These studies have shown no inferiority of laparoscopic colon resection as compared to open surgery regarding cancer-free survival. Colonic surgery is performed by general surgeons or by surgeons with a subspecialisation in colorectal surgery. The importance of such surgical specialisation has been debated. There are data supporting that colorectal subspecialisation has an impact on the prognosis for patients with colorectal cancer. Regarding the value of a high operative volume, some authors have shown that high volume centres have a better outcome than low volume centres, and some studies have related a better outcome to specific high volume surgeons. The impact of caseload and speciality for the outcome in colorectal cancer has not been clearly established, and there is currently a Cochrane Collaboration protocol aiming to clarify this.

Recovery
The postoperative in-hospital stay after colonic resection is usually 6-12 days. After a colon resection, the patient has classically been immobilised for several days with postoperative ileus, nausea and pain. In recent years, much attention has been brought to using a multidisciplinary approach with a focus on stress reduction and promotion of return to function. The ERAS (Enhanced Recovery After Surgery) group is a collaborative of five Departments of Surgery from five Northern European countries. It was formed in 2001 and has established a protocol that aims at allowing patients to recover quickly from major surgery, avoiding decline in nutritional status and fatigue and reducing the hospital stay. The ERAS protocol involves a number of pre-, per- and postoperative aspects, summarized in Table 1. The laparoscopic approach in colon cancer surgery has shown a decrease in postoperative ileus and hospital stay as compared to open surgery, but further assessment of the effect of laparoscopic surgery in addition to the ERAS protocol is warranted.

Histopathologic staging
Correct staging of the disease is important to predict prognosis and to select patients for adjuvant treatment. Different staging systems have been suggested for the classification of colon cancer. The most widely used is the Dukes’ classification for rectal cancer, launched by Cuthbert Dukes in 1932. This system considers the depth of tumour penetration into the bowel wall and the involvement of lymph nodes (Dukes’ A-C). This classification has been modified repeatedly and in 1939 it was extended for use in colon cancer. In 1967 a category for patients with distant metastases was introduced (Dukes’ D). In order to introduce a standardized and more detailed system, the American Joint Commission of Cancer (AJCC) has developed the TNM system (Tumour, Node, Metastasis) for colorectal cancer,
applying criteria from the Union Internationale Contre le Cancer (UICC). The TNM system provides uniformity for staging cancer in all anatomic sites. The T-stage indicates the depth of local infiltration of the tumour into the bowel wall, the N-stage information on lymph nodes involved by the tumour and the M-stage information on distant metastases. The TNM system provides an AJCC/UICC stage classification that parallels the Dukes’ classification system. The relationship between the Dukes’ and TNM systems is shown in Table 2.

To provide the correct classification of the N-stage for colon cancer, it has been concluded that a minimum of twelve lymph nodes should be examined. This number has, however, been discussed, and some authors believe that 17 nodes is...
required whereas six nodes have been proposed to be sufficient by others \(^{101, 102}\). In a study from Uppsala, the index of metastases (IM), as derived from the number of lymph nodes with metastases divided by the number of nodes examined, was introduced as a prognostic factor. The study showed that the IM was a stronger prognostic factor for survival than the classic staging into N1 and N2, where N1 indicates the involvement of 1-3 nodes and N2 the involvement of \(\geq 4\) nodes (Table 2) \(^{103}\). The significance of such a ratio of metastatic to examined lymph nodes as a prognostic factor has later been confirmed \(^{104}\).

Traditionally, the nodes from a specimen are identified by manual palpation and examined by haematoxylin and eosin staining of serial sections. A large proportion of the metastatic lymph nodes are reported to be smaller than 5 mm and thus likely missed by manual palpation. To increase the identification rate of lymph nodes, another technique, fat clearance, can be used \(^{105}\). This is, however, time-consuming, labour intensive and thus expensive. Immunohistochemistry, with monoclonal antibodies against epithelial histology, is a pathology tool that surpasses the capabilities of routine staining. By identifying nodes with micrometastases, immunohistochemistry has been shown to upstage patients with node negative tumours according to routine examination by several authors \(^{106-108}\). The clinical importance of micrometastases is, however, debated \(^{106, 108-111}\). An even more sensitive method of finding very small deposits of tumour cells is the polymerase chain reaction (PCR) technique \(^{112, 113}\). The studies performed are small, and more studies are required to determine the clinical importance of this method.

The concept of a sentinel node (SN) was first introduced regarding cancer in the parotid gland \(^{114}\). In the 1990s it was applied to melanoma and breast cancer \(^{115, 116}\). A difference between the use of SN in these mentioned tumours and in colon cancer is that, in the former two cancers, the SN can limit the extent of resection, whereas in colon cancer it rarely would affect the planned operative resection, but could rather allow a more thorough pathologic examination of this specific node. The two methods of identifying the SN are injection of visible dye and lymphoscintigraphy. Dye and/or isotope is injected subserosally around the tumour and is, within minutes, transported by lymphatic vessels to one or a few lymph nodes, the sentinel nodes. This can be done intraoperatively in vivo or ex vivo when the specimen has been resected. Some authors report a high sensitivity and specificity \(^{117}\). Others show more pessimistic results and the value of SN in colon cancer is still in doubt \(^{118, 119}\).

The tumour status regarding local and distant residual tumour after surgery is described by the residual tumour (R) classification, proposed by the UICC in 1987 (Table 3). It has been shown that a better prognosis is strongly correlated to an R0 resection, with total tumour clearance.
### Table 2. Systems for classification of colon cancer

<table>
<thead>
<tr>
<th>AJCC/UICC staging system</th>
<th>TNM system</th>
<th>Dukes’ classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1-2 N0 M0</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>T1=Invasion of submucosa</td>
<td>Tumour limited to the bowel wall</td>
</tr>
<tr>
<td></td>
<td>T2=Invasion into, but not through, the muscularis propria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N0=No nodal metastasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M0=No distant metastasis</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>T3-4 N0 M0</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>T3=Penetration through the mucosa into subserosa, or into non-peritonealized pericolic tissues</td>
<td>Penetration through bowel wall without nodal involvement</td>
</tr>
<tr>
<td></td>
<td>T4A=Invades other organ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4B=Perforates visceral peritoneum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N0=No nodal metastasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M0=No distant metastasis</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>Any T N1-2 M0</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>N1=Metastasis in 1-3 regional lymph nodes</td>
<td>Lymph node metastasis</td>
</tr>
<tr>
<td></td>
<td>N2=Metastasis in ≥4 lymph nodes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M0=No distant metastasis</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T Any N M1</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>M1=Distant metastasis</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

### Table 3. Residual Tumour Classification

<table>
<thead>
<tr>
<th>R-CLASS</th>
<th>Tumour status</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>No residual tumour</td>
</tr>
<tr>
<td>R1</td>
<td>Microscopic residual tumour</td>
</tr>
<tr>
<td>R2</td>
<td>Macroscopic residual tumour</td>
</tr>
</tbody>
</table>
Adjuvant medical oncologic therapy and radiation

In the 1980s, several trials were performed regarding adjuvant treatment with chemotherapy after potentially curative surgery for colorectal cancer \(^{120, 121}\). An analysis of these trials shows that there is a 10-12 per cent gain in 5-year survival with adjuvant 5-fluouracil-based (5-FU) treatment after surgery for stage III colon cancer. Chemotherapy for patients with stage III colon cancer is thus a part of standard therapy since the 1990s. Regarding stage II colon cancer, the efficacy of chemotherapy remains equivocal. There are data suggesting that adjuvant chemotherapy should be offered to patients with “high risk” stage II tumours, for example T4 tumours, poorly differentiated tumours, perforated cancers or cases where an insufficient number of lymph nodes (<12 nodes) have been found in the specimen \(^{122-124}\).

A previous study has shown that a high expression of thymidylate synthase predicts a higher sensitivity to 5-FU-based chemotherapy \(^{125}\). In the future, molecular profiling of the tumours may identify individuals more likely to benefit from adjuvant treatment and thus make it possible to tailor the adjuvant treatment individually.

More recent studies have concluded that the addition of oxaliplatin or irinothecan to the 5-FU regimen improves survival, but at the expense of more toxic side effects, such as neutropenia and peripheral neuropathy \(^{126, 127}\).

As shown in rectal cancer treatment, radiotherapy applied to adenocarcinoma of the bowel is efficient \(^2, 4, 5, 128-130\). However, in the case of colon cancer, the use of radiation has been restricted to locally advanced tumours, since a large amount of small intestine is affected by the radiation, with a risk for subsequent problems with diarrhoea and mechanical obstruction due to radiation damage \(^{131-134}\). There are no prospective trials on preoperative radiotherapy for resectable colon cancer. Previous studies on other gastrointestinal tumours indicate that preoperative neoadjuvant treatment with chemotherapy or radiation is more effective than postoperative treatment \(^{135-137}\), but no studies have evaluated preoperative chemotherapy to patients with colon cancer.

Follow-up

Whether or not an intensive follow-up program contributes to an increase in overall survival, after potentially curative resection for colon cancer, has been the topic of several studies \(^{138-143}\). The objective for follow-up includes a better overall survival, psychological reasons for the patients and scientific or quality control purposes for the healthcare system. Many cohort and case-control studies have supported the benefit of follow-up, but the protocols of randomised trials have been heterogeneous and shown ambiguous results \(^{140, 141, 143-145}\). A Cochrane review concludes that follow-up of patients does increase survival, but the details of the optimal follow-up
Background

regimen still need clarification. For this purpose an international multicentre-trial, COLOFOL, has been launched, in which several Swedish institutions participate. The co-ordinating centre is in Aarhus, Denmark.

Recurrence

Metastases

Colon cancer has the potential to spread by direct extension of the primary tumour, lymphatic flow, haematogenous, trans-coelomic or implantation. At the time of diagnosis, approximately 50 per cent of the patients have metastases in the regional lymph nodes. Colon cancer may spread to all organs, such as the liver, lung, ovaries, adrenal glands, brain and skeleton. Tumour spread in the peritoneum is also common, but it can be debated to what extent this spread should be considered as distant metastases or as loco-regional recurrence. According to follow-up studies, the overall risk for recurrence after potentially curative surgery for colon cancer is 26-57 per cent. Isolated recurrences can be cured if an operation with complete removal of the tumour can be accomplished.

The most commonly reported site for distant metastases is in the liver. The reason for this is the direct venous drainage from the colon to the portal vein system. According to previous reports, 8.1-31 per cent of patients operated on with a potentially curative resection for colon cancer later develop hepatic metastases. There are reports from specialized institutions of hepatic surgery that the primary resectability rates of all, synchronous and metachronous, hepatic metastases is 20-25 per cent. By down-sizing chemotherapy, the resectability rate may, according to some authors, increase to 30-40 per cent of all hepatic metastases from colorectal cancer. Population-based studies on the treatment of liver metastases and resectability rates are, however, scarce, and data from referral centres are limited due to recruitment bias.

Hepatic resection is accepted as the only treatment modality with a potential for cure. The reported 5-year survival after hepatic resection is 30-71 per cent, whereas the 5-year survival without surgery is essentially non-existent. Chemotherapy alone may prolong the survival of patients with irresectable disease. Several other treatment modalities, such as cryotherapy, radiofrequency ablation and stereotactic radiation, have been reported. These methods are currently being evaluated, but none have so far proven to be curative.

In most cases of metastatic colon cancer, the prognosis is poor. When a complete resection is impossible, palliative care, with or without medical oncologic treatment or palliative radiation, should be undertaken.
**Loco-regional recurrence**
The definition of local recurrence from colon cancer is equivocal. Some authors define it as a recurrence located in the tumour bed of the primary tumour, and some include all extra-hepatic abdominal recurrences\(^1\). The interesting point is that since local recurrences must be caused by tumour cells left behind locally during surgery for the primary tumour, the local recurrence rate is generally considered to be a measure of the quality of the primary surgery. Since recurrences in parenchymal abdominal organs are probably caused by haematogenous spread, it is reasonable to exclude them from the definition of loco-regional recurrence and define loco-regional recurrence as abdominal recurrences in non-parenchymal organs, thus indicating that these recurrences may be caused by suboptimal surgery. Population-based studies specifically directed towards loco-regional recurrences from colon cancer are scarce, and the incidence is unclear. Previous authors have reported loco-regional recurrence rates of 3.1-48 per cent after potentially curative operations for colon cancer\(^1\).

**Survival**
Some published survival data on colon cancer are derived from specific centres and not from populations, making comparisons with other studies difficult. It is generally accepted that for stage I colon cancer, surgery results in a relative 5-year survival rate close to 100 per cent\(^1\). Figure 3 shows the relative survival according to stage for patients diagnosed with colon cancer in the Stockholm-Gotland region during 1996-2000. Regarding patients with stage II tumours, it has been previously shown that a higher number of examined lymph nodes correlates with a better 5-year survival\(^1\). For patients with stage III tumours, the relative 5-year survival rate in Stockholm is about 55 per cent. In patients with more than three metastatic lymph nodes, the proportion surviving 5 years is about 15 per cent less than for patients with a maximum of three positive nodes. According to previous studies, grouping the patients according to index of metastases or lymph node ratio gives an even larger difference in survival rate\(^1\). The relative 5-year survival rate for patients with stage IV disease is less than 5 per cent.
Quality registers

Quality assurance in surgical oncology is a major concern for all healthcare units and for patients. It has been shown that quality assessment improves outcome \(^{184, 185}\). Quality registers are built up by a systematic sampling of case record forms in local, regional or national databases.

Since 1958, data on all patients with cancer in Sweden are reported to the National Cancer Registry by the responsible physician and by the pathologist at the time of diagnosis. Causes of death are reported to the Cause of Death Registry at the National Board of Health and Welfare. The Stockholm County Council keeps records of all healthcare consumption including diagnoses according to the International Classification of Diseases (ICD) of the World Health Organisation.

The Stockholm Colorectal Cancer Study Group (SCCSG), consisting of surgeons, medical and radiation oncologists, pathologists and radiologists, was set up in 1980 with the aim of improving outcome in colorectal cancer. As part of this program, a database with prospectively collected data on all patients in the Stockholm-Gotland region, diagnosed with an invasive adenocarcinoma of the colon, was initiated in 1996. This registry, managed by the Oncologic Centre in Stockholm, includes detailed information on age, sex, tumour location and stage, emergent or elective surgery, type of surgery performed, postoperative mortality, radiotherapy, chemotherapy, the histopathology of the tumour, tumour length, width and thickness according to the pathologist and follow-up data on recurrence and survival.

![Figure 3. Relative survival in 2775 patients with colon cancer in the Stockholm-Gotland region 1996-2000](image-url)
With the intention to initiate a project aiming to improve the management and outcome of patients with colon cancer, the specific aims of this thesis were

- to review overall results after treatment for colon cancer in a population-based cohort, with special reference to potential differences between hospitals

- to report incidence, management and outcome for patients with loco-regional recurrence from colon cancer and to identify risk factors for loco-regional recurrence

- to assess the potential for an increase in the hepatic resection rate and thereby improve the outcome for patients with hepatic metastases from colon cancer in the Stockholm-Gotland population

- to determine whether tumour volume is a prognostic factor in patients with colon cancer
Methods
Each resident in Sweden has a unique identification number, which has enabled the development of large population-based registries including different cancer diagnoses. All four studies in this thesis were based on data from the Oncologic Centre database, described on page 29. In the database, the colon is defined as the large intestine above 15 cm from the anal verge, excluding the appendix. As a part of the investigations performed for the studies included in the thesis, the data reported to the Oncologic Centre database were validated and updated through all registers previously described. When needed, medical records were reviewed.

The incidence rates reported from the National Board of Health and Welfare, as described on page 17, were somewhat higher than the absolute number of colon cancer patients in the studies of this thesis. This is attributable to the fact that the tumours reported to the National Cancer Registry also include adenomas with high-grade dysplasia, whereas this thesis only includes invasive adenocarcinoma.

Out of all patients diagnosed with colon cancer during 1996-2000, only 30 moved from the region during the follow-up period. Dates of death were available in these patients and they were included in the survival analyses. Regarding the evaluation of recurrence, these patients were censored at the date of moving from the region, when follow-up data on recurrence could not be retrieved.

During the study period, there was no standardized protocol for routine postoperative follow-up of patients with colon cancer in the Stockholm-Gotland region, and thus follow-up routines differed between hospitals.

The patients included in each paper are displayed in Figure 4.

Statistical methods
The chi-square test was used to establish the significance of differences in distributions. P-values <0.05 were considered statistically significant. The Kaplan-Meier method was used to estimate survival. Survival times were calculated from the date of primary surgery until the date of death or end of follow-up or, in non-operated patients, from the date of diagnosis until death or end of follow-up (Paper I and IV). When analysing survival after tumour recurrence, the survival times were
calculated from the date of diagnosis of the recurrence until death or end of follow-up (Paper II and III). A Cox proportional hazards regression model was used to assess risk factors for death (Paper I and IV) or loco-regional recurrence (Paper II and IV). In these multivariable analyses, adjustment was made for case mix including age, sex, tumour node metastasis stages and emergent or elective surgery (Paper I) as well as tumour location, bowel perforation and tumour differentiation (Paper II and IV) and also including local completeness of the surgery (Paper IV). Resulting hazard ratios (HR) are presented with 95 per cent confidence intervals (CI).

Figure 4. Patients with adenocarcinoma of the colon included in the papers.
Colon cancer management and outcome in relation to individual hospitals in a defined population (Paper I)

Patients
All 2855 patients who were diagnosed with colon cancer in the Stockholm-Gotland region between January 1996 and December 2000 were included. They were followed until January 2005. In 80 patients the tumour was diagnosed at autopsy and these patients were excluded from further analysis, leaving 2775 patients eligible for follow-up. The outcome was analysed in relation to the nine hospitals in the region responsible for colon cancer management.

Results
The 2775 patients in this study had a median age of 74 years. The clinical characteristics of all patients are displayed in Table 4. There were significantly more right-sided tumours in women (669/1430) than in men (526/1345) and left-sided tumours were more common in men (651/1345) than in women (577/1430). Surgery was performed in 2706 (98%) patients. The proportion of electively operated patients was 2116 (78%) and 590 (22%) patients had an emergent operation. A potentially curative operation was accomplished in 1901/2775 (68%) patients. Out of the curative operations, 1549 (81%) had an elective procedure and 352 (19%) an emergent one.

Table 4. Patient characteristics in 2775 patients diagnosed with colon cancer in the Stockholm-Gotland region 1996-2000

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1345 (48)</td>
</tr>
<tr>
<td>Female</td>
<td>1430 (52)</td>
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<tr>
<td>Tumour location</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1195 (43)</td>
</tr>
<tr>
<td>Transverse</td>
<td>281 (10)</td>
</tr>
<tr>
<td>Left</td>
<td>1228 (44)</td>
</tr>
<tr>
<td>Multiple</td>
<td>65 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
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<tr>
<td>Tumour stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>332 (12)</td>
</tr>
<tr>
<td>II</td>
<td>1043 (38)</td>
</tr>
<tr>
<td>III</td>
<td>753 (27)</td>
</tr>
<tr>
<td>IV</td>
<td>572 (21)</td>
</tr>
<tr>
<td>Unknown</td>
<td>75 (3)</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>2116 (76)</td>
</tr>
<tr>
<td>Emergent surgery</td>
<td>590 (21)</td>
</tr>
</tbody>
</table>
Recurrence and survival
The median survival time for all 2775 patients was 50 months, with a crude cumulative 5-year survival of 46 per cent. The importance of a complete clearance of the tumour at primary surgery is shown in Figure 5. The crude 5-year survival was significantly better, 61 per cent, in patients who had a curative operation according to the surgeon and the pathologist than if one of them expressed uncertainty or, even worse, if both were uncertain or one of them considered the surgery incomplete. The risk for death after emergent surgery was significantly higher than after elective procedures, with a hazard ratio of 1.68 (95% CI 1.45-1.96). This increase was seen even after excluding all deaths within six months, and thus excluding deaths due to postoperative complications in the emergent setting.
Outcome in relation to hospital
Survival analyses showed differences in overall survival depending on at which hospital the operation had been performed (Fig. 6). When adjusting for age, sex, TNM stage and emergent or elective surgery, some differences remained. Differences were also shown regarding risk for subsequent diagnosis of local recurrence. Better or worse results did not correlate with any special category of hospital, i.e. university hospitals versus community hospitals or high volume as opposed to low volume hospitals.

Figure 6. Crude survival in 2608 patients after abdominal surgery for colon cancer in nine hospitals in the Stockholm-Gotland region.
Loco-regional recurrence from colon cancer: a population-based study (Paper II)

Patients
All 1856 patients, who were submitted to a potentially curative resection of a colon cancer in the Stockholm-Gotland region between January 1996 and December 2000, with a survival of more than 30 days postoperatively, were included. They were followed until January 2005. The medical records of all patients diagnosed with an abdominal recurrence in a non-parenchymal organ were reviewed. Data on sex, age, elective versus emergent surgery, bowel perforation, T-stage, N-stage, tumour location and grade of differentiation were analysed in all patients to assess risk factors associated with the development of a loco-regional recurrence.

It was recorded whether the recurrence was found due to presence of symptoms or at routine examination. The management of the recurrence was studied and the outcome analysed.

Results
The cumulative 5-year incidence of loco-regional recurrence was 11 per cent (Fig. 7). A loco-regional recurrence was detected in 193/1856 patients, after a median time of 18 months.

Figure 7. Cumulative incidence of loco-regional recurrence after potentially curative resection for colon cancer.
Risk factors
In a multivariable analysis, emergent surgery, more advanced T- and N-stages, perforation of the bowel and a poor differentiation of the tumour were identified as independent risk factors for later development of loco-regional recurrence (Table 5). Tumours in the right flexure had the highest risk for loco-regional recurrence, followed by tumours in the sigmoid colon, as compared to all other locations. In Table 6 the number of lymph nodes examined in the specimen in relation to the different tumour locations is displayed. A larger proportion of patients with tumours in the sigmoid colon had only 0-3 lymph nodes examined, compared to tumours in other locations.

Clinical characteristics and management
In 136/193 patients (70%) the loco-regional recurrence was located in the same abdominal quadrant as the primary tumour. One recurrence was diagnosed at autopsy and this patient was excluded from further analysis. In 161/192 patients (84%) the loco-regional recurrence was discovered due to symptoms, and in 31 (16%) it was found at routine follow-up (Table 7). As has been previously mentioned, during the study period there was no standardized routine follow-up protocol. In the majority of the patients, 122 (64%), the loco-regional recurrence was the first tumour manifestation and in 91 (48%) it remained the only one.

In Figure 8 the treatment of all patients with loco-regional recurrence is displayed. A surgical procedure was performed in 110 (57%) patients. Of these, 17 (15%) had been preoperatively evaluated by a multidisciplinary team, with at least a surgeon and an oncologist. The surgery was performed as an elective procedure in 65 (59%) patients and as an emergent procedure in 45 (41%). It was planned with a curative intent in 49 patients and this goal was achieved in 21. In two additional patients, the recurrent tumour could be completely resected during emergent surgery due to bowel obstruction and thus, a total of 23/192 (12%) patients had a potentially curative treatment. An incomplete resection was performed in 39 patients and palliative procedures without resection in 48. All patients with loco-regional recurrence at the end of follow-up had symptoms, mainly abdominal pain and mechanical obstruction.

Survival
The median survival for the 192 patients with a locally recurrent colon cancer was nine (range 0-72) months from the date of diagnosis of the recurrence. In the 23 patients where a potentially curative resection of the recurrence had been performed, the estimated 5-year survival was 43 per cent, whereas no patient in the other groups had survived five years at the end of follow-up.
Table 5. Multivariable analysis of risk factors for diagnosis of loco-regional recurrence after potentially curative colon cancer surgery. Adjusted Hazard ratios adjusted for tumour location, bowel perforation, elective/emergent operation, T-stage, N-stage and tumour differentiation

<table>
<thead>
<tr>
<th>Factors analyzed</th>
<th>All patients (N=1856)</th>
<th>Patients with loco-regional recurrence (N=193)</th>
<th>Crude Hazard ratio</th>
<th>95% Confidence interval</th>
<th>Adjusted Hazard ratio</th>
<th>95% Confidence interval</th>
</tr>
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<td>Caeicum</td>
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<td>41</td>
<td>1.46</td>
<td>0.85-2.50</td>
<td>1.38</td>
<td>0.80-2.38</td>
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<td>295</td>
<td>20</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Right flexure</td>
<td>118</td>
<td>19</td>
<td>2.74</td>
<td>1.46-5.14</td>
<td>2.56</td>
<td>1.36-4.82</td>
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<tr>
<td>Transverse colon</td>
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<td>16</td>
<td>1.23</td>
<td>0.64-2.38</td>
<td>0.97</td>
<td>0.50-1.89</td>
</tr>
<tr>
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<td>9</td>
<td>2.18</td>
<td>0.99-4.78</td>
<td>1.46</td>
<td>0.66-3.27</td>
</tr>
<tr>
<td>Descending colon</td>
<td>78</td>
<td>9</td>
<td>1.66</td>
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<td>0.65-3.23</td>
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<td>Sigmoid</td>
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<td>1.07-2.93</td>
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<td>127</td>
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<td>Emergent</td>
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<td>2.17-3.95</td>
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<tr>
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<td>49</td>
<td>14</td>
<td>3.38</td>
<td>1.92-5.94</td>
<td>1.97</td>
<td>1.08-3.59</td>
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<td></td>
</tr>
<tr>
<td>T1</td>
<td>107</td>
<td>2</td>
<td>0.08</td>
<td>0.01-0.56</td>
<td>0.20</td>
<td>0.03-1.52</td>
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<td>10</td>
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<td>1.00</td>
<td>Reference</td>
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<td>1.84-3.54</td>
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<td>1.43-2.81</td>
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<tr>
<td>N2</td>
<td>166</td>
<td>45</td>
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<td><strong>Differentiation</strong></td>
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<tr>
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<tr>
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<td>42</td>
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<td>21</td>
<td>2</td>
<td>-</td>
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</table>
Table 6. Number of lymph nodes examined in relation to tumor location in 1856 colon cancer specimens. Numbers in parenthesis are percentages

<table>
<thead>
<tr>
<th>Location</th>
<th>0-3 nodes</th>
<th>4-5 nodes</th>
<th>6-8 nodes</th>
<th>9-11 nodes</th>
<th>&gt;11 nodes</th>
<th>Missing</th>
<th>Total</th>
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<tr>
<td>Caecum</td>
<td>92 (22)</td>
<td>76 (18)</td>
<td>99 (23)</td>
<td>64 (15)</td>
<td>70 (17)</td>
<td>20 (5)</td>
<td>421</td>
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<tr>
<td>Ascending</td>
<td>51 (17)</td>
<td>53 (18)</td>
<td>76 (26)</td>
<td>42 (14)</td>
<td>64 (22)</td>
<td>9 (3)</td>
<td>295</td>
</tr>
<tr>
<td>Right flexure</td>
<td>26 (22)</td>
<td>20 (17)</td>
<td>28 (24)</td>
<td>16 (13)</td>
<td>20 (17)</td>
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<td>118</td>
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<tr>
<td>Transverse</td>
<td>56 (29)</td>
<td>35 (18)</td>
<td>48 (25)</td>
<td>28 (14)</td>
<td>22 (11)</td>
<td>6 (3)</td>
<td>195</td>
</tr>
<tr>
<td>Left flexure</td>
<td>18 (27)</td>
<td>19 (28)</td>
<td>11 (16)</td>
<td>9 (13)</td>
<td>7 (11)</td>
<td>3 (5)</td>
<td>67</td>
</tr>
<tr>
<td>Descending</td>
<td>21 (27)</td>
<td>18 (23)</td>
<td>17 (22)</td>
<td>11 (14)</td>
<td>9 (11)</td>
<td>2 (3)</td>
<td>78</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>215 (31)</td>
<td>126 (18)</td>
<td>162 (24)</td>
<td>73 (11)</td>
<td>79 (12)</td>
<td>27 (4)</td>
<td>682</td>
</tr>
</tbody>
</table>

Table 7. Initial dominating symptoms and findings in 192 patients with loco-regional recurrence after colon cancer. Numbers in parenthesis are percentages

<table>
<thead>
<tr>
<th>Symptoms/clinical findings</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>75 (39)</td>
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<tr>
<td>Mechanical obstruction</td>
<td>46 (24)</td>
</tr>
<tr>
<td>Bleeding/Anemia</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Palpable mass</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Urogenital symptoms</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Colonoscopy/Barium enema</td>
<td>13 (7)</td>
</tr>
<tr>
<td>CEA level increased, no symptoms</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>9 (5)</td>
</tr>
</tbody>
</table>
The potential for improved outcome in patients with hepatic metastases from colon cancer: a population-based study (Paper III)

Patients
All 2280 patients who were diagnosed with colon cancer in the Stockholm-Gotland region between January 1996 and December 1999 were included. They were followed until January 2002. The patients with hepatic metastases were followed until January 2003. The medical records of all patients with hepatic metastases were reviewed regarding management and outcome. To assess the number of patients with potentially resectable hepatic metastases, all patients younger than 80 years of age, without signs of extrahepatic disease and surviving more than 30 days after the diagnosis of hepatic metastases, were selected. Available CT or MRI examinations were evaluated retrospectively. Patients with a maximum of four metastases were regarded as potential candidates for hepatic surgery, and medical records were studied to assess whether they had been evaluated for hepatic resection.
**Results**

*Management and survival*

Liver metastases were diagnosed in 537 (24%) of the 2280 patients. They were synchronous in 343 (15%) and metachronous in 194 (8%) patients. In 29 patients the metastases were found at autopsy and they were excluded from further analysis, leaving 508 patients eligible for follow-up. Figure 9 shows the evaluation of all patients.

In 242 patients concomitant extrahepatic disease was present. Out of these, 84 had chemotherapy, four in combination with stereotactic radiation or ethanol injections. One had stereotactic radiation alone, whereas the other 157 patients had symptomatic treatment only. The median survival for these 242 patients was 3.5 (range 0-51) months.

Hepatic metastases was the only tumour manifestation in 266 patients. The treatment of these patients is displayed in Table 8. A potentially curative hepatic resection was performed in 21 patients. In 13 of these, surgery was combined with chemotherapy, stereotactic radiation, radiofrequency ablation or local ethanol injections. Eleven

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**Figure 9. Evaluation of patients with hepatic metastases from colon cancer.**

*Two patients submitted to hepatic resection were found in this group.*
(52%) out of the 21 patients who had undergone surgery were alive after a median follow-up time of 29 (range 13-45) months, eight without evidence of disease. Of the ten patients who died during the follow-up time, two died from complications related to the hepatic surgery. The other eight all had recurrent metastatic disease in the liver.

The retrospective evaluation of 177 patients fulfilling the selection criteria for possible surgery showed that 66 patients out of 114 with available films of CT/MRI investigations had a maximum of four metastases (Fig. 9). Out of these, 44 were evaluated by a hepatic surgeon and 19 were submitted to liver surgery. The fact that two patients were missing from the total number of 21 patients who had surgery as described above, was due to missing CT/MRI in these patients. The assessment of all medical records and available CT/MRI showed that an additional 19 patients might have been candidates for liver surgery.

Table 8. Treatment of 266 patients with isolated hepatic metastases from colon cancer in the County of Stockholm

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>No of patients</th>
<th>Alive at follow-up Dec 31 2002</th>
<th>Median follow-up time* (range)</th>
<th>Alive with NED‡ No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>8</td>
<td>5</td>
<td>25 (13-45)</td>
<td>4</td>
</tr>
<tr>
<td>Surgery + stereotactic radiation</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Surgery + chemotherapy</td>
<td>8</td>
<td>5</td>
<td>38 (13-44)</td>
<td>4</td>
</tr>
<tr>
<td>Surgery + ethanol + chemotherapy</td>
<td>2</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Surgery + RFA</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Surgery + chemotherapy + RFA</td>
<td>1</td>
<td>1</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Stereotactic radiation</td>
<td>6</td>
<td>1</td>
<td>49</td>
<td>1</td>
</tr>
<tr>
<td>Radiation + chemotherapy</td>
<td>5</td>
<td>2</td>
<td>(31-39)</td>
<td>0</td>
</tr>
<tr>
<td>Radiation + ethanol + chemotherapy</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>76</td>
<td>3</td>
<td>37 (13-58)</td>
<td>0</td>
</tr>
<tr>
<td>Ethanol + chemotherapy</td>
<td>5</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>No active treatment</td>
<td>152</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

*Follow-up time (months) in patients alive Dec 31 2002
‡ NED; No Evidence of Disease
Tumour volume as a prognostic factor in colon cancer (Paper IV)

Patients
All 1865 patients, who had an abdominal resection of a colon cancer in the Stockholm-Gotland region between January 1996 and December 2000 and where tumour length, width and thickness were measured and reported, were included in this study. The three measurements were multiplied to calculate a volume in cm³. Depending on their volume, the tumours were then subdivided into three categories: small, medium and large. The groups were defined so that all groups included a similar number of patients. Survival analyses were performed for the different volume categories. Multivariable analyses, with adjustment for other known prognostic factors, were performed to evaluate tumour volume as an independent prognostic factor for survival.

Results
The survival analysis of the patients in the three volume groups showed a significantly better survival for patients in the “small” group and a significantly worse survival in the “large” group as compared to the “medium” group (Fig. 10). After excluding patients with stage IV disease, a multivariable analysis showed that tumour volume was an independent prognostic factor for survival, recurrence-free survival and

![Graph showing overall survival in 1865 patients with colon cancer in relation to tumour volume.](image)

Figure 10. Overall survival in 1865 patients with colon cancer in relation to tumour volume.
loco-regional recurrence, when adjusting for factors known preoperatively (Table 9). A difference persisted between small and large tumours, even after adjusting for all factors known postoperatively: sex, age, tumour location, emergent or elective surgery, local completeness of the surgery, TNM-stage, bowel perforation and grade of differentiation.

Table 9. Tumour volume as a risk factor for overall death, any tumour recurrence and loco-regional recurrence for stage I-III colon cancer in relation to preoperatively known variables. Adjustment was made for sex, age, tumour location and emergent or elective surgery. Hazard ratios (HR) are presented with 95% confidence intervals.

<table>
<thead>
<tr>
<th>Tumour volume</th>
<th>No. of deaths</th>
<th>Overall death</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small (≤15.0 cm³) n=573</td>
<td>248</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Medium (15.1-41.9 cm³) n=517</td>
<td>255</td>
<td>1.25 (1.05-1.49)</td>
<td></td>
</tr>
<tr>
<td>Large (≥42 cm³) n=495</td>
<td>276</td>
<td>1.62 (1.36-1.94)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour volume</th>
<th>No. of any recurrences</th>
<th>Any tumour recurrence</th>
<th>No. of loco-regional recurrences</th>
<th>Loco-regional recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small (≤15.0 cm³) n=573</td>
<td>127</td>
<td>1.00 (reference)</td>
<td>61</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Medium (15.1-41.9 cm³) n=517</td>
<td>123</td>
<td>1.25 (1.05-1.48)</td>
<td>59</td>
<td>1.16 (0.81-1.66)</td>
</tr>
<tr>
<td>Large (≥42 cm³) n=495</td>
<td>141</td>
<td>1.59 (1.34-1.89)</td>
<td>85</td>
<td>1.99 (1.42-2.79)</td>
</tr>
</tbody>
</table>
DISCUSSION AND FUTURE PERSPECTIVES

Data collection
Research based on registries involves a risk for errors due to poor validity in the registries. The registries cannot rely solely on the reports from surgeons or other physicians, since the compliance is variable and the data is sometimes incorrect. For example, it has been shown that complications from colorectal cancer surgery are incompletely reported. Quality registers must thus be continuously validated and updated. Increased use of population-based registries for research purposes presumably increases the validity and overall quality through such validation. It is of importance that the registries are used to ensure and improve quality and not merely audit the results.

The database that forms the basis of this thesis has continuously been submitted to validation by a data manager at the Oncologic Centre. As part of the work of this thesis, the database has been thoroughly validated through comparison to all available registries on healthcare consumption and diagnoses, as described on page 29. Extensive studies of medical records have been performed to minimize the errors in the registry. During this validation, it was apparent that the data initially reported to the registry were mainly correct, but not complete. In comparison to the National Cancer Registry, the Oncologic Centre database lacked reports from about one per cent of all patients with colon cancer. It was thus completed by retrospective collection of data on these patients. Regarding follow-up data on tumour recurrence, the Oncologic Centre database lacked reports on about 25 per cent of tumour recurrences. This was found by comparing with the other registers mentioned and by reviews of medical records that were undertaken due to registered healthcare consumption. It is reasonable to believe that most clinically relevant recurrences have been reported to the database at the Oncologic Centre, to the Stockholm County Council Registry or have been mentioned in the medical records and have thus been included in the studies of this thesis.

Management
As the survival for rectal cancer patients in Sweden, after intense efforts in clinical research on adjuvant radiotherapy and educational initiatives regarding surgery, is now slightly better than for colon cancer, it is time for action towards improved management of patients with colon cancer.
The studies in Paper I-III are overviews of the management and outcome of colon cancer in the region and cannot with certainty give specific answers as how to improve outcome. However, with these studies as a background, some issues can be discussed.

**Preoperative staging**

During the study period of this thesis, in the Stockholm-Gotland region, a protocol for preoperative evaluation has been established regarding metastases in the liver and lungs. However, local staging of the primary tumour has only rarely taken place. Also, the fact that over 20 per cent of all patients with colon cancer have emergent surgery makes it obvious that a large part of the patients have not been submitted to a thorough preoperative evaluation. As shown in Paper I and by other authors, a crucial factor for survival is the achievement of a complete tumour clearance at primary surgery. To accomplish this, a preoperative assessment of the primary tumour and a thorough management plan to minimize the number of patients who have an incomplete resection according to either the surgeon or the pathologist should be of value. It seems crucial to intensify the multidisciplinary collaboration between the surgeons and radiologists for a better preoperative staging. As part of these efforts, in Paper IV we investigated the possibility of prognosticating survival with the help of tumour volume. This showed that tumour volume could be of value as a prognostic factor and should be further investigated, along with other efforts towards a better preoperative staging. It may be argued that this study is flawed since it uses the tumour volume as measured from the resected specimen to assess this variable as a prognostic factor in the preoperative setting. However, it has been shown previously, for rectal cancer, that tumour volume may be measured on MRI with a good correlation to the histopathological assessment. It is likely that tumour volume in colon cancer may be accurately assessed by MRI or CT and also that the relation between increasing tumour volume and adverse prognosis is unrelated to the method of measurement. Studies on preoperative MRI in patients with colon cancer, including local staging and the correlation of radiological and histopathological assessments of tumour volume in Stockholm, are ongoing. The management of patients with colon cancer may change if these studies prove MRI to be accurate in the local staging and if the results from Paper IV can be reproduced on tumour volume measurements from MRI or CT. New radiological methods, such as positron emission tomography combined with CT (PET/CT), may also prove to be of value in planning the management because of the integrated functional and anatomic information. Another interesting non-invasive imaging technique is diffusion-weighted MRI (DW-MRI). This technique allows characterization of biologic tissues on the basis of water diffusion and evaluates the diffusion process in vivo, depicting different speeds of diffusion with different signals as seen on the
MRI. The essence of this technique is that the speed of diffusion of water molecules is different in intracellular and extracellular tissues. Intracellularly, the diffusion coefficient is decreased due to the presence of cellular membranes, cytoskeleton and organelles. Malignancies generally have a high cellular density and may thus be discriminated from healthy tissues (Fig. 11). This has been shown in single studies and will be an interesting field of development. Preoperative mapping of the tumour may change the surgical strategy by improved planning of the procedure, including multiple organ resections in locally advanced tumours.

Figure 11.
a. T2-weighted MRI of a patient with colon cancer. The polypoid tumour (arrow) in the ascending colon has a higher signal intensity than the surrounding propria muscle without any evidence of extramural or locally advanced disease. A small lymph node adjacent to the tumour is also detected.
b. Diffusion-weighted MRI at the corresponding level shows an area of localised decreased intensity possibly representing a high cell density within the tumour compared to the surrounding tissues. The image contains functional information but not anatomic details.
c. The functional diffusion-weighted image is colour coded and superimposed on the anatomic T2-weighted image, which facilitates localisation of the tumour and the lymph node with decreased diffusion signals.
Surgery
During the past 20 years, the surgical technique for rectal cancer has evolved, including a thorough dissection in embryological planes, with removal of all mesorectal fat, including the lymph nodes; the total mesorectal excision (TME). This has radically reduced the local recurrence rate and improved survival after rectal cancer surgery. Colon cancer surgery is considered less demanding than rectal cancer surgery and as such has been a matter for general surgeons without a specific colorectal interest and often for residents. An approach similar to the TME concept, a total mesocolic excision, is now being discussed regarding colon cancer. A better survival than in the Stockholm-Gotland population has been reported after extensive and meticulous dissection of the mesocolic lymph nodes and more effort should perhaps be made in achieving a wide mesocolic excision 79, 190, 191 (Fig. 12). There is no reason to believe that a meticulous sharp dissection in anatomical planes should be of less importance in colon cancer than in rectal cancer surgery.

Figure 12. Specimen from right hemicolectomy. A wide mesocolic excision with long vascular pedicles.
Histopathological staging
In Paper I, the histopathological examination showed that the majority, 1043 (38%), of the patients had stage II disease. It is, however, important to note that the median number of examined lymph nodes during the study period was six, which is lower than recommended in the current management protocol in the region. This low number of lymph nodes conveys a risk of patients being misclassified as having stage II tumours when, in fact, they have stage III disease. This could be due to suboptimal surgery, suboptimal histopathology or probably both. Since the time period of the studies of this thesis, the lymph node harvest has improved in the Stockholm-Gotland region and in 2005 the median number of lymph nodes examined in colon cancer specimens was 14 (Table 10).

The pathologist also plays an important role in the quality assessment of the surgery performed. In rectal cancer surgery, the pathologist inspects the specimen and categorises it as to whether a complete TME has been performed and whether the mesorectal fascia is intact without tears. This same approach should be used in evaluating the colon cancer specimen and thus be an incentive for the surgeon to strive for the perfect specimen.

<table>
<thead>
<tr>
<th>Year</th>
<th>Median number of lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>5</td>
</tr>
<tr>
<td>1997</td>
<td>6</td>
</tr>
<tr>
<td>1998</td>
<td>6</td>
</tr>
<tr>
<td>1999</td>
<td>7</td>
</tr>
<tr>
<td>2000</td>
<td>7</td>
</tr>
<tr>
<td>2001</td>
<td>9</td>
</tr>
<tr>
<td>2002</td>
<td>10</td>
</tr>
<tr>
<td>2003</td>
<td>10</td>
</tr>
<tr>
<td>2004</td>
<td>12</td>
</tr>
<tr>
<td>2005</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 10. Number of lymph nodes examined in colon cancer specimens in the Stockholm-Gotland region 1996-2005 (n=4945)
Adjuvant treatment

Studies on chemotherapy have shown that adjuvant chemotherapy increases survival in patients with stage III disease. Thus, it is important to achieve a correct staging of the patients, to offer adjuvant chemotherapy to patients whom it may benefit. Among the patients evaluated in this thesis, only patients with locally advanced, primarily non-resectable colon cancers received preoperative treatment with chemotherapy or radiotherapy. Previous studies on gastric cancer and rectal cancer have shown that preoperative, neo-adjuvant treatment with chemotherapy or radiotherapy respectively, leads to a better outcome than postoperative adjuvant treatment. This stresses the need for prospective randomised trials on neo-adjuvant treatment for patients with colon cancer. To select patients at high risk for recurrence for such a trial, it is of importance to prognosticate the outcome preoperatively. As has previously been mentioned, there is no reliable method of staging patients with colon cancer preoperatively regarding T- and N-stage, but several methods are being evaluated. The tumour volume may be of value in prognosticating patients at high risk of recurrence, as shown in Paper IV. The differences between different volume groups diminished after adjusting for all postoperatively known factors. This is not surprising, since the histopathologic tumour stage and differentiation are well-known prognostic factors. However, the histopathologic data are only known postoperatively and the aim of this study was to evaluate whether tumour volume could render a way to assess prognosis preoperatively. Perhaps tumour volume could be one variable to take into account when selecting patients with a high risk for recurrence. Neo-adjuvant chemotherapy may then be given to patients with large tumours to induce downsizing, facilitate resection and improve the prognosis.

Recurrence

Loco-regional

In Paper II, loco-regional recurrence had a cumulative 5-year incidence of 11 per cent. This is higher than in some reports on local recurrence from rectal cancer. The definition of a loco-regional recurrence is however debatable. The definition used in Paper II, as all abdominal recurrences in non-parenchymal organs, has the advantage of minimising the risk of excluding true local recurrences due to differences in the reporting of recurrences to the Oncologic Centre database or the Stockholm County Council Registry. This definition catches local recurrences reported as distant metastases in the peritoneum or abdominal lymph nodes. Both higher and lower incidences of loco-regional recurrences from colon cancer have been previously reported. This can in part be explained by different definitions of local or loco-regional recurrence, partly by differences in follow-
Discussion and future perspectives

up and probably also by true differences in abdominal recurrences. The previous
reports have not been population-based and this may have affected the results due
to selection of patients.
The location of the primary tumour in the right flexure has not previously been shown
to be related to an increased risk for loco-regional recurrence, although location in
the sigmoid colon has \(176, 177, 201\). One hypothesis about why these locations are risk
factors is that tumours in the right flexure or sigmoid colon may have a higher risk
of an incomplete regional nodal clearance. Most patients with tumours in the right
flexure had a right hemicolectomy, probably sparing the left branches of the middle
colic vessels. This could lead to an incomplete evacuation of regional nodes along
these vessels. When evaluating the number of lymph nodes examined in relation
to tumour location, the number of examined nodes in these patients was not lower
than for others, but this might be explained by the fact that a large number of lymph
nodes of less importance for tumour clearance were removed along the ileocolic
vessels. Regarding tumours in the sigmoid colon, most patients were operated on
with a sigmoid resection, saving the inferior mesenteric vessels, which also might
have led to an incomplete nodal clearance. This was supported by the fact that a
higher proportion of patients with tumours in the sigmoid colon had a very small
number of lymph nodes examined compared to the other tumour locations.
Paper I showed some inter-hospital differences in risk for local recurrence. This
analysis was performed with data on local recurrence as reported to the Oncologic
Centre database by the responsible surgeon or oncologist, and not with the wider
inclusion criteria for loco-regional recurrence used in Paper II. However, when
performing the study on loco-regional recurrence in Paper II, the multivariable
analysis made regarding local recurrence in Paper I was performed anew, with
the definition of loco-regional recurrence as all abdominal recurrences in non-
parenchymal organs. This analysis yielded the same result regarding which hospitals
had a higher risk for loco-regional recurrence as the analysis of local recurrence
in Paper I, indicating that the difference seen was not due to differences in the
definition of loco-regional recurrence in different hospitals.
As local failures from rectal cancer are generally considered to be caused by sub-
optimal surgery, the same reasoning could be applied on loco-regional recurrence
from colon cancer, once again emphasizing the importance of a complete tumour
clearance at primary surgery. The study in Paper II included only the patients
where both the surgeon and the pathologist agreed on a complete tumour clearance.
Outside of the study, a review was made including all patients in the Stockholm-
Gotland region 1996-2000, with colon cancer stage I-III. This showed that the
estimated 5-year incidence of loco-regional recurrence, when one of the surgeon
or the pathologist had expressed uncertainty about the resection margins, was 34
per cent, whereas when one or both reported incomplete resection margins, the loco-regional recurrence rate was 55 per cent. One can argue that if the primary resection is incomplete, 100 per cent of the patients should have recurrences or progressive tumour growth and this may be true. One explanation may be that if the resection is apparently incomplete, no efforts are made to diagnose an abdominal recurrence and only some, probably the ones that are clinical problems for the patients, are diagnosed or reported. A large proportion of these patients also had distant metastases, perhaps overshadowing a loco-regional tumour growth.

Metastases
As shown in Paper III, only four per cent of the patients (21/508) with hepatic metastases were submitted to hepatic resection during the study period. This proportion is remarkably low. The retrospective evaluation of CT and MRI implied that a total of 50 patients (10%) might have been candidates for surgery. From an international perspective, this proportion is still low.

It is estimated that preoperative chemotherapy would render 30 per cent of primarily irresectable metastases resectable. If all patients in this study who were not considered suitable for primary hepatic resection would have been eligible for down-sizing chemotherapy, another 38 patients might have been candidates for liver surgery, adding up to a total of 88 (50+38) patients with resectable metastases, i.e. 17 per cent of the 508 patients. This number is still low but yet it is an over-estimation, since many of the patients who were not suitable for immediate surgery had concomitant diseases, excluding them from surgery and chemotherapy.

Since hepatic resection is still considered the only potentially curative treatment for metastases to the liver, an increase in the hepatic resection rate would be desirable. Although not shown in this study, an optimised management with multidisciplinary conferences, treatment protocols and possibly routine follow-up would probably increase the resection rate. However, in an unselected population with a high median age, as in the Stockholm-Gotland region, it is probably hard to reach the resection rates of 30-40 per cent that have been reported from specialized centres.

Survival
Since 1996 the Stockholm-Gotland region has a joint management protocol for colon cancer. Thus, it could be expected that patients managed in the different hospitals should have very similar results regarding survival. Paper I shows that this was not the case. There were differences in overall survival. Most differences did not reach statistical significance, but were consistent over time, indicating that they were not random. It is, however, important to note that there may be confounders, such as concomitant diseases and differences in socio-economic status in the region.
Discussion and future perspectives

that may have an impact on survival. It can be debated whether or not a region of this size should have colon cancer surgery performed in nine different hospitals. The larger hospitals had a volume of 60-90 patients with colon cancer annually, while three hospitals had less than 25 per year. This study did not show a difference in survival related to hospital volume, as has been reported by previous authors. The expertise of the surgical team and the pre- and postoperative management are likely very important, although the studies in this thesis cannot determine the most important factors.

Paper I showed a worse prognosis for patients who have emergency surgery rather than elective surgery. This has been previously reported. Whether this is caused by patient-related factors and/or by poor surgery in the emergent setting is unclear. A prospective study from Spain, where all elective and emergent surgery was performed in a standardized way by the same colorectal surgeons, still showed some differences in outcome, although overall survival after curative resection of stage II colon cancer did not show a statistically significant difference in emergent or elective cases.

Further improvement

The Stockholm TME project for rectal cancer was initiated in 1994, with workshops including live operations and lectures. This project has proven successful in improving the outcome for patients with rectal cancer. A similar project for colon cancer, “The Colon Cancer Project in Stockholm”, was initiated in 2004. This project aims at improving the management and outcome for patients with colon cancer through a multidisciplinary approach. It includes repeated workshops with discussions on the current management protocols in and outside of the Stockholm-Gotland region. Routines for radiology, surgery, histopathology, medical oncology, radiotherapy and follow-up are conferred. There is an emphasis on future perspectives and the possibilities for improvement of all parts of the management of patients with colon cancer. Ongoing studies on MRI and CT for local staging of colon cancer can hopefully shed some light on the possibilities of preoperative local staging.

The colon cancer project also includes educational initiatives to improve the surgery, with live demonstrations of colon cancer operations. The surgical aim is a sharp exact dissection in embryological layers to achieve a complete resection of the mesocolic segment without tears in the specimen. Efforts to optimise the histopathological staging after surgery are ongoing. The low number of lymph nodes reported in the studies of this thesis has already improved, but further improvement and collaboration with the pathologists is desirable. After correct histopathological staging, adjuvant treatments should be considered in multidisciplinary conferences. In the studies of
this thesis, the value of multidisciplinary teams has been discussed repeatedly. It is important to point out that the results of the studies cannot determine the efficacy of such multidisciplinary teamwork. However, to achieve an improvement in the outcome for the large group of patients with colon cancer, every small part of the management needs optimising. To accomplish this, it seems necessary to have close collaboration between all the specialists involved in the management to move, step-by-step, towards a better outcome for these patients.
• The overall 5-year survival for patients with colon cancer in the Stockholm-Gotland region during 1996-2000 was 46 per cent. The survival was highly correlated with the completeness of the primary surgery.

• Despite a common management protocol, there were differences in overall survival for patients with colon cancer in different hospitals in the Stockholm-Gotland region. There were also differences in the risk for local recurrence.

• The cumulative incidence of loco-regional recurrence from colon cancer in the Stockholm-Gotland region during 1996-2000 after potentially curative surgery was high (11%). Most recurrences were located in the same abdominal quadrant as the primary tumour.

• Out of 192 patients with loco-regional recurrence, more than half (57%) underwent surgery for the recurrence, but only a small proportion (12%) of the 192 had a potentially curative operation.

• The median survival for all patients with loco-regional recurrence was less than one year. The only treatment with a potential for cure was a complete surgical resection of the recurrence.

• The hepatic resection rate for patients with hepatic metastases from colon cancer diagnosed during 1996-1999 was low (4%). A re-evaluation of all available CT/MRI examinations indicated that the resectability rate may have been at least doubled.

• Tumour volume is a prognostic factor in colon cancer. Whether this factor is usable in clinical practice needs to be evaluated in prospective studies.

• The Colon Cancer Project in Stockholm has been launched to approach and hopefully reach the aim of our research effort: to improve the management and outcome for patients with colon cancer.
Areas of further studies

AREAS OF FURTHER STUDIES

• Preoperative staging. How can it be improved?

• Neo-adjuvant treatment. Can it improve the outcome?

• Emergent surgery. Why are the results bad and what can be done about it?

• Gender perspective. Do men and women receive the same treatment for colon cancer?
Koloncancer (tjocktarmscancer) är en av de vanligaste tumörformerna i världen. Det finns en stor geografisk variation i förekomsten, med högst frekvens i Västeuropa och Nordamerika och lägst i Afrika och i södra Asien. Sverige har en hög incidens och i Stockholms län insjuknar årligen 500-600 personer i koloncancer. De flesta tumöråterfallen kommer inom fem år.

Koloncancer drabbar framför allt äldre personer och medianåldern vid insjuknande i Stockholm är 74 år. Det finns ett fåtal patienter med specifika ärfältiga syndrom som får koloncancer i unga år, men sjukdomen är annars mycket ovanlig före 40 års ålder.

Vårdprogram och kvalitetsregister


Utredning och diagnos

De flesta fall av koloncancer upptäcks p.g.a. symptom från tumören. Symptomen kan vara magsmärtor eller ändrade avföringsvanor med förstoppning, diarré, blod eller slem i avföringen. Blödningen kan i sin tur ge järnbrist, som yttrar sig som trötthet. Utredning med kolonröstgen eller fiberoptisk undersökning av kolon, koloskopi, ger diagnosen. Det finns studier som talar för att överlevnaden kan förbättras genom s.k. screening, där man på symptomfria personer i vissa åldersgrupper undersöker om...
det finns blod i avföringen. Sådan screening har dock ännu inte införts rutinmässigt i Sverige. Efter diagnos utreder man med hjälp av röntgen om det finns tecken till metastaser i levern eller lungorna, vilka är de vanligaste metastaslokalisationerna.

**Behandling, stadieindelning och överlevnad**

Kururgi med borttagande av all synlig tumörvävnad utgör den enda möjligheten till bot. Man avlägsnar då den del av kolon där tumören sitter och kopplar ihop tarmändarna igen. Tarmsegmentet med tumören skickas för mikroskopisk undersökning för att erhålla en stadieindelning av tumören enligt det s.k. TNM-systemet (Tumour Node Metastasis), där T anger hur djupt tumören växer i tarmväggen, N visar om det finns tumör i lymfkörtlarna och M anger om det finns fjärrmetastaser. Stadieindelningen är av vikt för att bedöma prognosen och behovet av eventuell tilläggsbehandling.

Om mikroskopisk undersökning visar tumörväxt i lymfkörtlar ges som regel tilläggsbehandling med cellgifter för att öka chansen till bot. Cellgiftsbehandlingen är dock behäftad med biverkningar som äldre människor eller personer med andra sjukdomar kan ha svårt att tåla.

Vid fjärrmetastaser finns en möjlighet till bot om man kan operera bort metastaserna. Prognosen för majoriteten av de patienterna är dock dålig.

Tumörstadiet är den viktigaste prognostiska faktorn för överlevnad. Efter justering för den förväntade dödligheten är 5-årsöverlevnaden efter koloncancerdiagnos i Stockholm kring 60%. Överlevnaden är kraftigt beroende av vilket tumörstadium patienten haft.

**Delarbete I**

**Delarbete II**

Lokalrecidiv av koloncancer kan ge besvärande smärtor, infektioner och tarmvred. Beträffande frekvensen lokalrecidiv efter behandling för ändtarmscancer, som man arbetat aktivt med att minska, har man i Stockholmsregionen nått ned under 9% risk för lokalt återfall. Syftet med delarbete II var att kartlägga frekvensen av lokalrecidiv efter koloncancer i regionen samt undersöka hur de har behandlats. Hos 1901 patienter som opererats till synes kurativt för koloncancer 1996-2000 var femårsrisken att drabbas av lokalrecidiv 11%. Av dessa hittades 84% p.g.a. symptom från sitt lokalrecidiv, oftast magsmärta eller tarmvred. Risken för lokalrecidiv var högre vid vissa tumörlokalisationer i tjocktarmen, samt vanligare vid mer avancerade tumörstadier och i de fall där den primära operationen för koloncancer hade utförts akut. Medianöverlevnaden efter att diagnosen ställts var nio månader. Av 192 patienter med lokalrecidiv opererades 110 (57%) p.g.a. sitt recidiv. Hos 23 patienter lyckades man till synes avlägsna all tumörvävnad vid operationen och i denna grupp var den estimerade 5-årsöverlevnaden 43%. I gruppen där man inte lyckades få bort all tumörvävnad hade ingen överlevt i fem år och alla dessa patienter hade besvärande symptom från sina recidiv.

**Delarbete III**

Delarbete IV

Det mest avgörande för en god prognos vid koloncancer är att man vid primäroperationen lyckas ta bort all synlig tumörväv med marginal, en så kallad R0 resektion. Det vore önskvärt med en preoperativt mätbar prognostisk faktor för att förutse svårigheter att åstadkomma en R0 resektion samt att patienten ska ha lymfkörtelmetastaser eller risk för att senare utveckla lokala recidiv respektive fjärrmetastaser. I delarbete IV har vi studerat tumörvolymen, beräknad genom multiplicering av längd, bredd och tjocklek, som prognostisk faktor vid koloncancer. Vid överlevnadsanalyser utföll tumörvolymen som oberoende riskfaktor för återfall och död. Fortsatta studier för att klarlägga den kliniska användbarheten av tumörvolym som prognostisk faktor pågår nu.

Vad händer nu?

År 2004 startade ”Koloncancerprojektet i Stockholm” som syftar till att förbättra behandling och resultat för patienter med koloncancer. Projektet är multidisciplinärt med deltagande kirurger, onkologer, röntgenläkar och patologer. Informationen i föreliggande avhandling ger kunskap inför planeringen av den fortsatta strategin för att optimera omhändertagande och behandling av patienter med koloncancer.
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A. Sjövall


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