Colorectal Cancer

Audit and Health Economy in Colorectal Cancer Surgery in a Defined Swedish Population

PIA JESTIN
Dissertation presented at Uppsala University to be publicly examined in Auditorium Minor, Museum Gustavianum, 753 10 Uppsala, Friday, November 25, 2005 at 09:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

Colorectal cancer is one of the most common malignancies in Sweden, with more than 5000 new cases annually. Median age at time of diagnosis is approximately 75 years. Owing to the ageing population, the incidence of colorectal cancer is increasing. The improvement in surgical technique and the introduction of adjuvant radio- and chemotherapy increased the 5-year survival rate from approximately 30-40% in the early 1960s to almost 60% in the late 1990s. The cost of public health care has risen considerably, and case-costing systems are increasingly demanded. Linked to clinical guidelines and quality registers, such control systems form a proper basis for quality assurance projects and improvement. The aim of this thesis is to describe the efficiency and cost effectiveness of colorectal cancer treatment in a defined Swedish population. Emergency surgery for colon cancer, constituting 25% of the cases, increased both mortality and cost. Among emergency cases there was not only an increase in postoperative mortality but also a stage specific decrease in long-term survival rate. Correct staging is decisive for further treatment of patients after colon cancer surgery and influences long-term survival. The number of lymph nodes examined varied between different pathology departments and could be used as a quality measurement. The proportion of tumour stage III increased the more nodes examined. A prognostic estimation of stage III cases that is less sensitive to the number of nodes examined is proposed. A case-control study aimed at identifying risk factors for anastomotic leakage after rectal cancer surgery confirmed previously known risk factors but failed to identify further steps during the perioperative course that were amenable to improvement. This research has confirmed that population-based quality and case-costing registers, linked to clinical guidelines, constitute a proper source for projects of quality improvement and decisions about distribution of resources in health care.

Keyword: colorectal cancer, colon cancer, rectal cancer, epidemiology, quality assurance, quality control, health economy, survival, hospital category, emergency surgery, lymph nodes, tumour staging, anastomotic leakage, case-control study, surgical complications

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“We can’t all, and some of us don’t.
That’s all there is to it.”

- Eeyore

“Pooh’s little instruction book” by A. A. Milne.
List of papers

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


IV Risk factors for anastomotic leakage after rectal cancer surgery, a case-control study. Jestin P, Pålman L & Gunnarsson U, manuscript.

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# Abbreviations

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<tr>
<td>APR</td>
<td>Abdominoperineal resection</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CPP</td>
<td>Cost per patient</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<td>DH</td>
<td>District hospitals</td>
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<td>EBM</td>
<td>Evidence-based medicine</td>
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<tr>
<td>FAP</td>
<td>Familial adenomatous polyposis</td>
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<td>GDH</td>
<td>General district hospitals</td>
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<tr>
<td>HNPCC</td>
<td>Hereditary non-polypsis colorectal cancer syndrome</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IM</td>
<td>Index of metastasis</td>
</tr>
<tr>
<td>LAR</td>
<td>Low anterior resection</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>RC</td>
<td>Relative cost</td>
</tr>
<tr>
<td>ROC</td>
<td>Regional Oncological Centre</td>
</tr>
<tr>
<td>Tis</td>
<td>Tumour in situ</td>
</tr>
<tr>
<td>TME</td>
<td>Total mesorectal excision</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumour Nodes Metastasis</td>
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<tr>
<td>UH</td>
<td>University hospitals</td>
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</table>
Introduction

Colorectal cancer is one of the most common malignancies world-wide, but its incidence shows considerable geographical variation, with differences up to 30-fold between different population groups [1]. The incidence rates of colorectal cancer are low in the African countries and South Asia, whereas the highest rates are found in North America, Australia and the Western European countries. These differences appear not to be due solely to genetic factors, since populations migrating from low- to high-incidence regions show an increase in the incidence of this cancer. Previous epidemiological studies have suggested that dietary factors play important causative and protective roles in the development of colorectal cancer. Fat intake has been the most consistently positive association noted and fibre intake the most consistently inverse association [2]. Although fibre has a strongly protective effect against colorectal cancer, the specific food categories related to this effect are poorly defined [3]. More recent studies have pointed to other food-related agents as protective against colorectal cancer [4-6].

In Sweden colorectal cancer is the third most frequent tumour, with an incidence of more than 5000 new cases annually [7], and after lung cancer it is the second most frequent cause of cancer death. Approximately one-third of the tumours are situated in the rectum and two-thirds in the colon. An increase in incidence has been observed during the past years in the Western countries, and has been mainly attributable to an increase in tumours in the right colon. The incidence of colon cancer is slightly higher in women than in men, in contrast to rectal cancer, which is more common in men. Furthermore, the incidence increases with age; thus, as the population ages, the number of colorectal cancer cases can be expected to rise. The median age at diagnosis is approximately 75 years in Sweden. Most cases of colorectal cancer are considered to be sporadic, without any relation to defined hereditary genetic lesions. However, approximately 1% to 15% of colorectal cancers have a hereditary background, for example familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer syndrome (HNPCC) [8]. These hereditary tumours occur at younger ages than sporadic cases, often at 40 years of age or earlier. Furthermore, there are considerable variations in the incidence of hereditary cases between different geographical areas.
Diagnosis
A diagnosis of colorectal cancer is mostly based on the evaluation of a symptomatic patient. The symptoms may be non-specific, such as intermittent pain, bleeding, nausea and vomiting. Most often it is the detection of anaemia associated with fatigue that initiates an investigation. A definitive diagnosis is mostly established by endoscopy or barium enema. In rectal cancer, preliminary preoperative staging of the primary tumour is mostly achieved with trans-rectal ultrasound or magnetic resonance imaging (MRI) [9-13]. This preliminary staging will form a basis for the decision as to whether preoperative treatment with radiotherapy, chemotherapy or a combination of the two will be given. Metastases from colorectal cancer are first seen in the regional lymph nodes and later as haematogenous dissemination to the liver and lungs. Plain X-ray and ultrasonography are used for preoperative screening for distant metastases in the lungs and liver. The use of specific schedules for multi-slice computed tomography (CT) and MRI examinations is of increasing importance, especially since the results of surgery for distant metastases has improved [14, 15].

Emergency surgery
In different studies the proportion of cases of emergency surgery among patients operated on for colorectal cancer ranges from 8% to 34% [16-21]. Although most of these studies do not distinguish between colon and rectal cancer, emergency surgery is far more commonly undertaken for colon cancer and is rare for rectal cancer. Patients operated on as emergencies often have a more advanced tumour stage at diagnosis, and thus a decreased survival rate. Thus, a stage specific decrease in survival rate has also been reported in a few recent publications [22, 23]. However, little is known about reasons for the increased mortality after emergency surgery. Further studies based on data collected on a population basis are needed to identify risk factors and reasons for the increased morbidity and mortality in emergency surgery for colorectal cancer.

Screening
Screening for colorectal cancer has received increasing interest in recent years. If detected at an early stage, colorectal cancer may be cured and even prevented by removal of possible precursors such as adenomas. Early detection will probably also decrease the frequency of emergency surgery for colon cancer [24] and thereby reduce the morbidity and mortality. Different screening methods, such as proteomics-based tests, stool genetic tests, faecal occult blood tests, radiological imaging, and endoscopy are under development or have been tested on groups of populations [25]. Issues of sensitivity, specificity and patient acceptance, however, limit the use of these methods. Introduction of screening programmes is still a subject of discussion, al-
though there are randomised trials demonstrating reduced mortality from colorectal cancer with the use of faecal occult blood tests [26-28].

*Treatment of colorectal cancer and surgical technique*

Surgery is the only curative treatment of colorectal cancer. Surgical options depend on the localisation of the primary tumour. With the introduction of the total mesorectal excision (TME) technique [29] for rectal cancer surgery, a new era began. The systematic development and improvement of this surgical technique in the last few decades have led to a substantial decrease in the local recurrence rate after rectal cancer surgery [30]. Recent results have now also revealed an increase in long-term survival [31-34]. During the past decade, the TME technique has become generally accepted. Several studies have indicated that the surgeon’s use of an optimal technique is one of the most important factors for the improvement of results [35, 36].

Before the introduction of the TME technique, rectal cancer surgery was mostly carried out with blunt dissection, thus entering the mesorectal envelope. The most important change with the TME technique is the mobilisation of the rectum, with sharp dissection under direct vision. The main principle is to follow the embryonic planes in the avascular cleavage outside the fascia rectalis and Denonvilliers’ fascia. With this technique the whole mesorectum can be excised without damaging the nearby important autonomic nerve plexuses. Tumours in the upper third of the rectum, more than 10 cm from the anal verge, can be resected with a subtotal mesorectal excision; that is, the mesorectum is divided horizontally at a minimum of 5 cm below the tumour. After the removal of the tumour-bearing part of the rectum, an anastomosis can often be performed to the rectal stump, hand sewn or with a staple intrument. In cases with very low tumours, less than 3-4 cm from the anal verge, the functions after these low anastomoses are often poor and it can be better to perform an abdominoperineal resection and a permanent sigmoidostomy.

Together with the TME technique, introduction of preoperative radiotherapy has considerably improved the outcome and survival. In a trial comparing pre- and postoperative radiotherapy [37] there was a significantly more pronounced reduction in the local recurrence rate after preoperative irradiation. In Sweden preoperative radiotherapy is mostly delivered either as a short-term schedule with 5 x 5 Gy in one week, mostly with operation within one week, or as conventional irradiation with 25 x 2 Gy up to 50 Gy for about 5 weeks and operation 4-6 weeks later. The irradiation is sometimes given in combination with chemotherapy. To compare these two strategies for radiotherapy, and to investigate the clinical relevance of downstaging of the tumour, and the influence of the length of time between the end of irradiation and surgery, a randomised trial is now in process, comprising patients with a primary resectable rectal cancer. The endpoints in this trial are...
local recurrence rate, postoperative morbidity and mortality, and long-term survival.

Whether or not such factors as the surgeon’s use of an optimal technique influence the survival rate after surgery for colon cancer, as has been demonstrated for rectal cancer, has been paid increasing attention in recent years, but has not yet been studied on a population basis. There are consecutive series from one centre showing increased survival with a more aggressive technique [38], but to provide scientific evidence further studies are required. The usual technique for colon cancer surgery is standardised segmental resections, depending on the location of the tumour; in this technique en bloc resection of the tumour-bearing colon segment together with the draining lymph nodes, including the lymph nodes at the origin of the respective main vessel, is mandatory. As the lymphoid drainage of the tumour is located along the vascular supply in the mesentery, it is important to dissect and divide the vascular trunk supplying the affected part of the colon as proximally as possible [39].

However, depending on the tumour location and stage, adjuvant chemotherapy has been shown to further improve survival. The relative survival rate increases 20-30% for colon cancer, stage III, when postoperative adjuvant chemotherapy is given [40, 41]. Further development of new and more potent drugs, with greater risks of immediate and late side effects, increases the demand for better tumour staging and guidance in the choice of drugs for each patient. This decision must be based on knowledge of who will benefit from each treatment [42].

In view of the advances in liver surgery for colorectal cancer metastasis and the decrease in postoperative morbidity and mortality after such surgery, it is becoming increasingly more important to perform a proper preoperative investigation of the liver [14, 15]. Even though most liver metastases are still unresectable, adjuvant chemotherapy can improve the survival and induce downstaging of the liver metastases, making surgery with curative intention possible in a few cases [43]. In patients with fewer liver metastases, located in one or two segments, the 5-year survival rate in radically resected cases is 30-40% [44]. Patients with local recurrence and a solitary lung metastasis should also be evaluated for the possibility of resection and adjuvant treatment [45].

Furthermore, there has been an intense debate regarding the optimal catchment area, caseload, subspecialisation, and concentration of resources to certain hospitals [46]. It is therefore important to determine whether surgeon-related factors are involved in the complication frequency and long-term outcome of colorectal cancer surgery.

Surgical complications of this type of surgery play an important role both from an ethical and from an economic perspective. Population-based studies may serve as a powerful tool in attempts to identify factors predisposing to surgical complications as well as for analyses of costs.
Pathology

Adenocarcinoma is the dominating form of colorectal cancer (accounting for more than 95%), and the remaining histological types are squamous cell carcinomas, lymphomas, sarcomas, malignant melanomas and carcinoid tumours. The present thesis is focused solely on the adenocarcinomas. Different systems have been used for classification of colorectal adenocarcinoma during the past years. Cuthbert Dukes, a pathologist at St. Mark’s Hospital in London, who initially devised a staging system for rectal cancer, introduced the most widespread system in 1932 [47]. During the past decade this system has been succeeded by the TNM classification [48], where T describes the degree of tumour penetration into the bowel wall, N the lymph node status and M the absence or presence of distant metastases (Table 1). There are different techniques whereby the pathologist can harvest regional lymph nodes from the specimen. It is essential however, to identify and examine the nodes where any primary dissemination might take place, i.e. to follow the main blood vessel according to the standardised resection performed (see above: “Treatment of colorectal cancer and surgical technique”). In rectal cancer the lymph nodes involved in the primary dissemination lie within the mesorectum, which is removed at the TME procedure. However, one problem is that preoperative radiotherapy often reduces the size of the lymph nodes and makes them difficult for the pathologist to identify. On the other hand, the patient's prognosis might be predicted by applying a classification of macroscopic completeness to a rectal resection specimen. According to Nagtegaal et al. [49] the pathologist’s ability to judge the quality of the TME performed can be of value as an interdisciplinary assessment instrument.

Survival

Considerable variations have been observed regarding stage at diagnosis and tumour-free survival between different geographical areas. Specific analyses of such differences are rare [3, 21, 50], partly because of difficulties in obtaining long-term follow-up data from large populations. Most published studies have provided data from specific centres [51, 52] or have focused on a specific question [22, 53]. From this perspective, Sweden is unique with its personal identity numbers offering the possibility of observing large population cohorts over long periods of time.

Overall, the 5-year survival rate for colorectal cancer is approximately 50% and the most important prognostic factor is the tumour stage at diagnosis.
Table 1. TNM classification of colorectal cancer, and survival rates by tumour stage (http://www.roc.se/).

<table>
<thead>
<tr>
<th>T – Primary Tumour</th>
<th>N – Regional Lymph Nodes</th>
<th>M – Distant Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>NX</td>
<td>MX</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
<td>N0</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: intra-epithelial or invasion of lamina propria</td>
<td>N1</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades the submucosa</td>
<td>N2</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades the muscularis propria</td>
<td>M0</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour penetrates through the muscularis propria into the subserosa or non-peritonealised pericolic or perirectal tissue</td>
<td>MX</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour directly invades other organs or structures and/or perforates the visceral peritoneum</td>
<td>M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
<th>5-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1, T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T3, T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>any T</td>
<td>N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>any T</td>
<td>any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
The survival rate for rectal cancer has been slightly lower than that for colon cancer. However, data from the Swedish Cancer Registry show that the 5-year survival rate for colon cancer improved from 40% in 1960-1964 to 57% in 1995-1999 and for rectal cancer from 31% to 58% in the corresponding period [34]. The fact that the 5-year observed and relative survival rates for rectal cancer are now comparable to those for colon cancer is probably a result of the implementation of the TME technique and preoperative radiotherapy.

Evidence-based guidelines

With their origin in Cochran’s systematic reviews and the establishment of national quality registers during the past two decades, evidence-based guidelines have been developed. Such guidelines are often linked to population-based quality registers and have become increasingly demanded in Swedish health care. Guidelines for colorectal cancer have been produced in consensus by surgeons, oncologists and pathologists and are continuously being revised. These guidelines summarise the most recent findings and put them into clinical practice, and include recommendations for specific methods for each step in the care of patients with colorectal cancer.

Quality registers and quality measurements

During the last decade, quality assurance in relation to results of surgery has become increasingly important. Many attempts to identify key variables and methods for measuring improvement have been made. Although outcome data can provide powerful insight into the question of where to target quality improvement efforts, hospitals need to identify influential and modifiable clinical practices, including development of practice guidelines based on group consensus or published recommendations [54]. It is also of great importance to involve clinicians in improvement projects, and to develop clinical education and training programmes [55].

Quality assurance projects have been built up as national, regional or local systems in many countries, often linked to different registers and to clinical guidelines. In colorectal cancer surgery, quality assurance is not a new field [56, 57], and some publications have focused on population-based audit of surgery from local, regional and national perspectives [21, 50]. It is also crucial that results derived from quality registers are validated for key variables [58].

In Sweden, quality assurance is by law a mandatory responsibility of each health care unit. An important part of this work is carried out with the aid of national quality registers specific for each major diagnosis. By virtue of the Swedish personal identity numbers, it is possible to link data from clinical studies in Sweden to data in the quality registers. Furthermore, linkage of data from other national registries run, for example by the National Board of
Health and Welfare, such as the national registry of causes of death or the cancer registry, can further improve analyses.

Use of such quality registers in epidemiological studies makes it possible to identify differences between geographical areas and to monitor changes over time in social and economic structures, as well as in medical treatment and outcome. When linked to clinical guidelines, quality registers can serve as a tool in the evaluation of new routines. Possible topics for such monitoring include, for example, diagnostic tests, surgical procedures and adjuvant or palliative treatments. For a specific hospital or department, the register can be used to compare their own results with those of their health care region or in some cases with national results. Such comparisons can be of value for pointing out areas that require more resources or treatments and units where the outcome needs to be improved.

Health economy

As a result of the high incidence of colorectal cancer and the consequently high use of health care services by the afflicted patients these patients constitute an important factor in health economy. Both the consumption of resources and the outcome of treatment vary, both on an international, national and regional level. In this field few studies have so far been published [59, 60], partly on account of the previously mentioned difficulties in achieving long-term follow-up of patients.

To be able to offer patients the best health care in a situation with diminishing resources, it is important to optimise the use and distribution of the resources available. Furthermore, there is a need to analyse the potential to equalise the differences in outcome within given limits.

There has been no widely accepted successful way of incorporating economic considerations into guidelines. In the USA it has been recommended that every set of clinical guidelines should include information on the cost implications of the alternative preventive, diagnostic and management strategies for each clinical situation [61]. In 1999 the Swedish Federation of County Councils started a nationwide project called the CPP (Cost per patient) project [62], with the overall aim of developing a system for calculation of costs in health care services. These costs should be linked to each patient and should be comparable between hospitals, diagnoses and patients. One important aim of the CPP project was to develop systems useful for each clinic in the control and follow-up of their own work. When collected and put together with the patient in focus, information about costs, considerations and treatments will be independent of the organisation and can then be compared between different units (Fig. 1).
The CPP model comprises four main steps:
1. To identify relevant costs for health care – what should be included?
2. To identify and distribute costs of joint activities.
3. To describe health care services and to calculate their costs.
4. To relate consumption of health care services to individual contacts with health care.

**Figure 1.** Outline of data collection in the CPP model.
Aims of the studies

The specific aims of the different studies were:

To describe the epidemiology, proportion of treatments carried out in accordance with guidelines, and health economy for colorectal cancer in one Swedish health care region. The primary hypothesis is that compliance to guidelines and costs differ in relation to hospital category (Paper I).

To identify risk factors and describe the outcome of emergency surgery for colon cancer, and to evaluate its effects on health economy (Paper II).

To determine the minimal number of nodes that need to be examined for a correct classification of colon cancer stage II. Furthermore, to investigate whether there is a relation between the number of lymph nodes examined (for tumour stages II and III) or the number of lymph nodes with metastases (for tumour stage III) and survival (Paper III).

To identify modifiable risk factors for anastomotic leakage after low anterior resection (LAR) for rectal cancer (Paper IV).
Material and methods

Subjects
The patients in Study I-IV were all prospectively reported to a population-based regional quality register, run by the Regional Oncological Centre (ROC), in the Swedish health care region of Uppsala/Örebro (in Study IV also the South-East health care region), for colon and rectal cancer. Entered in the registers are clinical data such as preoperative investigations, procedure of surgery performed, curative resection according to the surgeon’s opinion, postoperative complications if present, tumour stage according to the TNM classification, and further planning of possible adjuvant treatment. The register data are continuously checked against the regional cancer register to achieve maximal completeness of registration. Overall the completeness of these registers has reached a level of over 99%. Tumours (adenocarcinomas) located up to 15 cm from the anal verge are reported to the rectal cancer registry which started in 1995, whereas colon cancer cases are reported to a colon cancer register, started in 1997. Register data for rectal cancer are sampled also in the remaining five Swedish health care regions and aggregated on a national level. A corresponding national process for colon cancer has been initiated and is aimed to start in 2006. In Study I and II data for calculations of effects on health economy were derived from the national CPP register.

Paper I
Data for all patients operated on for colon cancer on an elective basis between 1997 and 2000 (n=1771) and for rectal cancer between 1995 and 2000 (n=1841) were taken from the ROC’s registers for colon and rectal cancer respectively, in the health care region of Uppsala/Örebro. For calculations regarding health economy, data were derived from the CPP register (1998-2000), comprising eight hospitals in different parts of Sweden. Standard procedures such as right-sided hemicolectomy, sigmoid resection, LAR and abdominoperineal resection (APR), without any registered postoperative complications, were selected for analysis.
Paper II

Data for all patients operated on for colon cancer between 1997 and 2001 (n=3296) in the health care region of Uppsala/Örebro were analysed. For 37 patients there was no information on whether the surgical procedure was elective or performed as an emergency and these patients were excluded from further analyses. Thus the remaining patients (n=3259) served as a basis for further calculations. Emergency surgery was defined as an urgent or emergency operation, performed for clinical reasons such as peritonitis, intra-abdominal abscess, severe bleeding or complete bowel obstruction.

For the calculations of health economy, data was taken from the CPP register. In this database the reason for hospitalisation was classified as emergency or elective, and thus served as the determinant, whereas the reason for the surgical procedure itself was the determinant in the ROC register. For patients operated on for colon cancer, the variable elective or emergency was recorded at seven units during 1999 to 2000 (n=1004). These data were included in further analyses.

Paper III

In this study all patients from the Uppsala/Örebro colon cancer register who had undergone any type of colon resection between 1997 and 2002 (n=3735) were included. According to the accreditation rules and common guidelines, information on the tumour stage, number of nodes examined and number of nodes with metastases is mandatory in the pathology report. Data were analysed in order to compare the quality of the pathology reports between different pathology departments and its importance for correct staging and survival.

Paper IV

To achieve acceptable power in this case-control study, patients from the ROC rectal cancer register in two Swedish health care regions, Uppsala/Örebro and the South-Eastern region, were included. In total 2896 patients were reported to the registry between 1995 and 2000. All patients who had undergone LAR (n=1381) were available for this case-control study from which cases and controls were selected. Cases (n=134) were all patients in whom an anastomotic leakage was registered as a postoperative complication (within 30 days postoperatively). Two controls were randomly selected for each case by the frequency matching technique (regarding age). The medical record of each patient (n=402) was scrutinised retrospectively and a study protocol was filled in.
Statistics

Statistica® software (SatSoft, Tulsa, USA) was used for statistical analyses. Distribution fitting of data was checked with the Kolmogorov-Smirnow test. Most parameters appeared to be normally distributed, with many patients in each group, whereas there were groups of variable size that did not fit in that distribution model. Thus, the non-parametric Mann-Whitney U test was generally used to calculate the significance of differences in continuous variables, and the Chi-2 test was applied in cases of dichotomous response parameters and to test differences in proportions between groups. Correlation was calculated by the Spearman rank correlation test. The Kaplan-Meier method was used to calculate cumulative survival rate. Differences in survival between groups were tested for significance by the log-rank method.

In Study II factors considered to be possible determinants of survival were first checked in univariate Cox proportional hazard regressions. The influence of the possible determinants was also tested in multivariate Cox proportional hazard regressions with 95% confidence intervals (CI) [63].

In Study IV, a cases-control study, the number of cases and controls were calculated so as to give a power of 80% with 5% significance. Two controls for each case were frequency matched for age with 10-year intervals. Variables considered as possible risk factors for anastomotic leakage were checked in univariate conditional logistic regression analysis. The influence of the possible determinants was also tested in a multivariate conditional logistic regression analysis [64].

Ethics

All studies were approved in advance by the local ethics committees. The quality registers themselves are not considered by the ethics committees, since they are a part of the quality assurance system which is mandatory by law and supervised by the National Board of Health and Welfare. However, the use of data for scientific studies shall be considered by the ethics committee, and this also includes matching against other relevant registers. The case-control study (Study IV) was considered separately by the ethics committee.
Results

Paper I

In the period studied there was a shift of patients from district hospitals (DH) to district general hospitals (DGH) for both rectal and colon cancer surgery, but the proportion of patients operated on at university hospitals (UH) did not change (Fig.2).

Figure 2. Trends in the proportion of patients operated on for rectal cancer (n=1841) and colon cancer (n=1771) at university hospitals (UH) ——, general district hospitals (GDH) ——, and district hospitals (DH) ——, respectively.

There was no difference in the proportions of different tumour stages in relation to hospital category. The proportions of TNM stages in colon and rectal cancer are shown in Table 2.

Preoperative staging differed between hospital categories. Investigation of colon cancer patients preoperatively with liver scan was less frequent at GDH (26%) than at UH (41%) and DH (57%). In rectal cancer patients, on the contrary, liver scan was less frequent at UH (34%) than at both GDH (54%) and DH (61%). Overall there was an increase over the studied period from 39% to 46% (p=0.02) in colon cancer and from 42% to 64% (p<0.001) in rectal cancer patients.
Table 2. Distributions of colon and rectal cancer patients by stage.

<table>
<thead>
<tr>
<th></th>
<th>Stage I n (%)</th>
<th>Stage II n (%)</th>
<th>Stage III n (%)</th>
<th>Stage IV n (%)</th>
<th>Stage unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td>241 (14%)</td>
<td>714 (40%)</td>
<td>499 (28%)</td>
<td>298 (17%)</td>
<td>19 (1%)</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>386 (21%)</td>
<td>515 (28%)</td>
<td>536 (29%)</td>
<td>300 (16%)</td>
<td>104 (6%)</td>
</tr>
</tbody>
</table>

Preoperative bowel examination differed, according to hospital category. This change in examination routine was most pronounced at DH, while it remained hardly unchanged at UH (data not published). Overall the proportion of barium enema decreased and the proportion of colonoscopy increased in patients younger than 75 years of age, electively operated (Fig. 3).

During the study period, the use of adjuvant preoperative radiotherapy in resectable rectal cancer decreased from 70% to 58% (p=0.04) among patients younger than 75 years of age. Hospital category was a determinant for the use of radiotherapy, with frequencies of 70% at UH, 51% at DGH and 70% at DH; the frequency at DGH differed significantly from the figures at UH and DH (p<0.001).
The proportion of patients younger than 75 years of age who were operated on for colon cancer stage III and were given adjuvant chemotherapy postoperatively as recommended in the guidelines, increased from 62% to 84% (p<0.001) during the study period.

We found no difference in 5-year survival rate between colon and rectal cancer (49% vs. 48% (p=0.2)). The mean lengths of follow-up were 2.6 and 3.0 years, respectively. Survival was independent of hospital category in both colon and rectal cancer in stage III.

Overall, the procedures for rectal cancer were more expensive than those for colon cancer, measured as relative cost calculated by the CPP method (1.4; 95% CI 1.3-1.5). In rectal cancer surgery, the APR procedure was more expensive than the LAR (1.2; 95% CI 1.1-1.2). There was no relationship between hospital category and the cost for a defined procedure. At an individual level, there was a significant correlation between the duration of hospital stay and cost for each surgical procedure (r² = 0.55; p<0.001). Hospital stay was overall shorter at UH (mean 8.9 days) than at DGH and DH (mean 11.4 and 12.0 days, respectively; p<0.001).

The redistribution of patients operated on for rectal cancer between 1996 and 1997 was probably due to specialisation among surgeons, general acceptance of the TME concept and the development of colorectal teams. The somewhat later corresponding change for colon cancer, however, was merely an effect of political decisions regarding health care structure. Compliance to guidelines varies between hospital categories and scientific development can influence local traditions before changes are made in the guidelines, as was observed for preoperative liver scan. Linked to case-costing data, these results can form a proper basis for decisions about health care planning.

Paper II

Using the criterion for emergency surgery given by the ROC colon cancer registry, the proportion of emergency procedures for cancer of the colon was 24.7%. No relation was found between hospital category and age at surgery, sex ratio, tumour stage or proportion of emergency procedures. However, perforation was a more frequent, and obstruction a less frequent indication for emergency surgery at UH compared to DGH.

A small but significant difference in age was seen between emergency and elective patients (mean 73.5 vs. 72.0 years; p=0.002). Patients having emergency surgery had a more advanced tumour stage than those operated on electively (4.2 vs. 14.9%, 33.7 vs. 40.9%, 35.4 vs. 27.3% and 26.7 vs. 16.9% for tumour stage I, II, III and IV, respectively; p<0.001 for all).

Emergency interventions were also associated with a lower rate of curative resections (559 of 806; 69.4%) compared to elective operations (2056 of 2726; 75.6%).
2453; 83.8%) (p<0.001). Surgical complications overall were more frequent among emergency cases (15.8 vs. 9.6%; p<0.001), as also was reoperation within 30 days postoperatively (9.7 vs. 5.0%; p<0.001).

The postoperative mortality rate (within 30 days after surgery) was higher after emergency than after elective intervention (10.2 vs. 2.5%; p<0.001). The median length of follow-up was 2.0 (range 0.0-5.3) years. The overall survival rate was lower in the emergency group than in the elective group (p<0.001) (Fig. 4).

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Compared with electively operated patients, emergency patients showed a stage-specific decrease in survival rate for the emergencies both when the analysis was performed separately for the first 6 months (p<0.001) and when the calculation was based on the remaining follow-up period (p<0.001) (Fig. 5).

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Elective</th>
<th>2453</th>
<th>1937</th>
<th>1286</th>
<th>846</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency</td>
<td>806</td>
<td>298</td>
<td>207</td>
<td>117</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4.** Kaplan-Meier analysis of overall survival and of elective and emergency procedures for colon cancer (p<0.001; log-rank test). Survivors are censored irrespective of the presence or absence of dissemination of the disease. The curves are censored when the number at risk falls to one-third of the initial population.
No. at risk
Elective, stage I + II 1288 1203 854 582
Emergency, stage I + II 249 218 147 90
Elective, stage III 576 499 331 206
Emergency, stage III 203 177 94 55

**Figure 5.** Kaplan-Meier analysis of survival in patients who underwent curative surgery for colon cancer. Patients who died during the first 6 months after surgery are excluded. Data are categorised to stage I + II and stage III, comparing elective and emergency procedures (p<0.001; log-rank test). Survivors are censored whether or not dissemination of disease was present. The curves are censored when the number at risk falls to one-third of the initial population.

The most important risk factor for death was tumour stage III (hazard ratio, HR 1.9 and 2.0 in univariate and multivariate analyses; both p<0.001). Male sex and perforation at surgery were both identified as risk factors in multivariate analysis (HR 1.3, p=0.004; and HR 1.3, p=0.037, respectively), but did not reach significance in the univariate analysis (HR 1.2, p=0.115; and HR 1.1, p=0.269, respectively). Surgical complications and reoperation were not found to be risk factors.

In the CPP database the proportion of emergency procedures was 33.3%. The duration of hospital stay was longer after emergency than after elective surgery (mean 18.0 vs. 10.0 days; p<0.001), which increased the cost of emergency procedures (relative cost, RC 1.5; 95% CI 1.4-1.6) compared to
elective. On an individual level, duration of hospital stay was the most important determinant of cost ($r^2 = 0.52; p<0.001$) and this correlation was reproducible for each specific procedure in each hospital category.

In this population-based study the proportion of emergency procedures for colon cancer was 25%. There was a stage-specific decrease in survival rate in patients having an emergency operation. This decreased survival rate was seen both when the analysis was performed separately for the first 6 months and when the calculation was based on the remaining follow-up period. In addition, patients operated on as emergencies had a more severe tumour stage, which further contributed to reduced survival in this group. The most important determinant for the increased cost of emergency surgery was the longer duration of postoperative hospital stay in these patients.

Paper III

In 64% (2390 out of 3735) of the patients the number of lymph nodes examined was stated in the pathology report. It was calculated from these reports that the median number of lymph nodes examined was 8 (mean 9.4), with a difference in medians between the seven pathology departments in the health care region ranging from 6 to 12 lymph nodes. However, during the study period there was an improvement in the percentage number of reports were the number of nodes examined was given (20% in 1997 and 90% in 2002) as well as in the number of nodes examined (median 6 in 1997 and 9 in 2002). Furthermore, the relative proportions of tumour stages II and III varied between the different pathology departments, with fewer stage II cases the greater the number of lymph nodes examined (Fig. 6).

Among patients with tumours of stage II, the survival rate was lower in patients in whom fewer than 12 mesenteric lymph nodes (as recommended in the guidelines) were examined, than in those in whom 12 or more nodes were examined ($p=0.001$, log-rank; median follow-up in survivors 40 months). The same difference in survival rate was seen when the cut-off was set to examination of 8 nodes (median in our material).

An index of metastases (IM, number of nodes with metastases divided by number of nodes examined) could be calculated in 733 (64%) of the 1151 patients with stage III tumours. The median IM was 0.32. Overall the survival rate was better among patients with IM <0.33 than in those with IM $\geq 0.33$ ($p<0.001$, log-rank). Also, among patients with stage III tumours, the survival rate was better in those with N1 tumours (1-3 positive nodes) than in patients with N2 tumours ($>3$ positive nodes); $p<0.001$, log-rank. N1 patients in whom 12 or more nodes were investigated or with an IM <0.33 had a better prognosis than those with fewer nodes or with IM $\geq 0.33$ (5-year survival rate 50-60% vs. 30-40%; $p<0.005$ for both comparisons).
In comparison of survival rates, larger differences were found when the patients were grouped by IM than by N stage (Chi-2 log-rank 39.1 vs. 27.0, in both cases \( p < 0.001 \)). IM was the strongest determinant for survival as calculated in a Cox proportional hazard model, including IM (<0.33 yes or no) and N stage (N1 vs. N2) (HR=3.18 [95% CI 2.18-4.64] and HR=1.03 [95% CI 0.99-1.07], respectively).

The number of lymph nodes that need to be examined for proper staging was dependent on IM. To evaluate the number of nodes that need to be examined, the proportions of cases with different IM correctly classified as stage III are presented in Figure 7. Thus, in this material, examination of 12 nodes was necessary to correctly classify cases with the median IM (0.32), whereas 20 nodes were necessary to ensure that 90% of the stage III cases would be identified with the lower quartile of IM (0.16).

**Figure 6.** Frequency of tumour stages II and III in relation to the median number of lymph nodes examined per pathology department.
We have found that cases classified as tumour stage II with fewer than 12 lymph nodes examined or where the number of nodes examined is not given are at higher risk of death than those with more than 12 nodes examined. The number of nodes examined is also of relevance in tumour stage III. The index of metastases can aid in decision making regarding the use of more potent adjuvant drugs, and can be superior to the N stage when lymph node sampling is insufficient.

Our conclusion from this study is that the quality of the examination of a colon cancer specimen, as measured by the number of lymph nodes examined, has an impact on the tumour staging and thus on the management of the patient.

Paper IV

Because of incorrect recording of the surgical procedure or of anastomotic leakage two cases and 28 controls were excluded from further analyses. Included were 132 cases and 240 controls.

The median age was 71 years and the male/female ratio was higher in the case group (1.9 vs. 1.2; p=0.023). The frequency of reoperation was higher in the case group than among the controls (48% vs. 2.5%; p<0.001) and the hospital stay was longer in the case group (median 19 days vs. 10 days, respectively; p<0.001). Postoperative mortality (within 30 days after surgery) was higher among cases than among controls (4.5% vs. 0.8%; p=0.018).

Male gender was a risk factor for anastomotic leakage in the univariate but not in the multivariate analysis (odds ratio, OR=1.30 [95% CI 1.04-1.63]
and OR=1.26 [1.00-1.58], respectively). In the multivariate analysis significant risk factors were ASA score >2 (OR=1.40 [1.05-1.83]), preoperative radiotherapy (OR=1.34 [1.06-1.69]), intraoperative events (OR=1.85 [1.32-2.58]), level of anastomosis <6 cm (OR=1.39 [1.01-1.90]) and severe bleeding (OR=1.45 [1.14-1.84]). A diverting stoma protected from leakage (OR=0.68 [0.52-0.88]).

None of the variables considered as possible targets for improvement, such as postoperative epidural anaesthesia, observation in an intensive care unit for more than 24 hours, and intraabdominal drainage, proved to be protective factors either in the univariate or in the multivariate analyses.

The most important risk factors for leakage were adverse intraoperative events, low anastomosis, and male gender. A diverting stoma is protective and can reduce the consequences when leakage does occur. Further analyses with focus on the surgical technique and on the individual surgeon may be valuable in identifying targets for improvement.
Discussion

One of the principal goals of this work was to investigate the quality and effectiveness of health care processes for patients undergoing colorectal cancer surgery and to identify different factors that can influence this quality. Another main purpose was to analyse health economic aspects of the care of these patients by comparing, for example, different surgical methods and different hospital categories. We have shown how evidence-based guidelines linked to population-based quality registers can be used in epidemiological and clinical studies aiming to improve the quality of modern health care. One main issue is to identify and clarify the different steps and modalities involved in the health care process of colorectal cancer. Using these above-mentioned registers as described in this thesis, different key variables and areas of interest have been pointed out as targets for potential clinical improvement. Together with health economy registers, such as the CPP register, this method is also an important tool for more specific analyses and distribution of health care resources.

Validity and reliability of the registers forming the basis for the improvement process are essential, and data from quality assurance of the registers themselves are prerequisites for a constructive process. A high degree of completeness and continuous validation of the registers are mandatory.

Methodological considerations

Clinical guidelines

Clinical guidelines should be used as a tool for clinicians in their everyday practice. Such guidelines need to be constructed from evidence-based medicine (EBM) [65, 66] and drawn up in multidisciplinary consensus, and should include all steps involved in the treatment process of the patient. Criticism against such a system is probably based on a mistaken view that EBM will interfere with the patients’ individuality and the physicians’ autonomy [67]. If clinical guidelines are continuously revised on the basis of newly acquired knowledge from clinical studies, they can be used in association with quality registers to permit an effective evaluation of the outcome.
Population-based registry

Since 1958 new cancer cases in Sweden have been reported to the Swedish Cancer Registry. This registry is based on reports from both the clinician and the pathologist. The completeness of the registry is 95-98% [68], and errors in the Swedish personal identity numbers are below 1% [69]. The ROC’s rectal and colon cancer registers are continuously checked against the Cancer Registry and their completeness is 99%. The different subgroups of these registers that were chosen for the present studies are all representative of a well-defined population, a fact that allows an unbiased selection.

Validation of the registers is fundamental, and the key variables chosen have to be declared valid to make the registry reliable [58]. An error frequency of below 5% for each variable registered is often considered valid. However, in the case of an uncommon occurrence, a very low frequency of errors could make the registration less valid [70, 71].

When linking data between different population-based registers, as was done in Studies I and II (the ROC colon and rectal cancer registries and the CPP register), it is important that all registers fulfil the criteria for population-based registers. However, even with such prerequisites fulfilled, possible effects of differences in catchment area and case-mix have to be taken into account.

Case-control study

In a case-control study, a number of cases and controls have to be selected according to the required power of the study. The cases are defined by the design of the study and the controls have to be randomly chosen from a representative cohort. One problem when matching the controls for any particular variable is that the variable used for matching cannot be analysed. For example, in our study of anastomotic leakage (Study IV) two controls for each case were frequency matched for age with 10-year intervals, and thus the age variable could not be analysed as a possible risk factor.

General discussion

Diagnostics and preoperative staging

Compliance to guidelines varied overall depending on the hospital category and type of variable, and over time. One example concerned the preoperative investigation of possible distant metastases, which changed considerably over the period studied (Study I) as a result of continuous discussions among surgeons of its value, together with the better results after liver surgery for metastases [14]. Another example of variability is in the preoperative bowel examination. The guidelines recommend colonoscopy for patients younger than 75 years of age, and barium enema for older patients. Implementation
of these recommendations considerably influences the use of resources. This redistribution of resources was seen at DH, where a significant increase in the relative number of colonoscopies was seen. At UH, however, no such increase was observed, probably as a result of insufficient resources (data not shown). Changes of this type and differences between hospital categories, or specific hospitals, can be used in calculations of costs and in discussions about future needs for resources.

Screening
In cohorts of patients included in screening projects, several studies have shown improved survival in colorectal cancer, and in addition cost effectiveness [26-28, 72]. One of the reasons for the improved survival is the higher rate of curable tumours as a result of increased early detection, which leads to a change in stage distribution with a higher proportion of stage I and II tumours. The reason for the decreased survival rate among colon cancer patients operated on as emergencies, described in Study II, is multifactorial. One reason is the more severe tumour stage in patients undergoing emergency surgery. Another reason is the increased postoperative mortality, which can partly be explained by the increased preoperative morbidity among those patients, many of whom present with bowel obstruction or perforation. Furthermore, the higher frequency of postoperative complications may be of indirect importance, although perforation and surgical complications were not risk factors in themself. However, the stage specific decrease in survival among emergency patients is more difficult to explain. Is the tumour biology different in tumours presenting as emergencies? Do these tumours grow more aggressively? To answer such questions further studies are required.

Introduction of a population-based screening programme is one possible way to decrease the number of patients requiring emergency surgery for colon cancer, and to increase survival. An analysis of the cost-effectiveness of screening programmes must thus include the increase in cost for an emergency procedure in comparison to an elective one.

Surgery
Surgical procedures for colorectal cancer are standardised according to tumour site and included in the guidelines. However, in each patient the preoperative investigation for detection of possible distant metastases and for loco-regional staging of the tumour in rectal cancer, is determining for the preoperative treatment.

In rectal cancer the surgical procedure can be, for example, a sphincter-saving procedure, i.e. LAR, or a procedure with a permanent stoma, i.e. APR. LAR is recommended in the guidelines for tumours that are more than 5 cm above the anal verge, and APR for tumours below that level, unless a 1-2 cm margin can be achieved. Some claim that the frequency of LAR
compared to APR can be used as an indicator of quality [73-75]. A possible explanation for the higher frequency of sphincter-saving procedures at UH and GDH compared to DH (Study I) may be an attempt at hospitals with fewer resources to avoid the increased risk of complications that is associated with very low anastomoses.

One of the most serious complications after LAR for rectal cancer is anastomotic leakage. Although the surgical technique in rectal cancer has improved, the frequency of anastomotic leakage remains at approximately 10% [76-78]. Some risk factors for this leakage are already known from earlier studies, such as male gender, low anastomoses and preoperative radiotherapy [76, 79, 80], although preoperative radiotherapy is debatable, as it has not been identified as a risk factor in randomised trials [37]. With the purpose of identifying other modifiable risk factors, e.g. type of irradiation, decisions taken during the perioperative course, and occurrence and methods of postoperative monitoring, with the aim of decreasing the leakage frequency, we designed the population-based case-control study presented in Paper IV. A randomised controlled trial does not seem to be a proper approach to fulfil these aims, as there are probably many subtle, multifactorial reasons for leakage. Rather, large epidemiological studies based on population-based registers are favoured methods. Although the medical record of each patient was scrutinised retrospectively to complement the registry data, we were unable to point to other risk factors than those already known. Possible reasons for the still substantial differences between units may be differences in supervising and training systems, differences in strategies not detectable in the register, and effects of the competence of each individual surgeon. These are interesting factors that might be possible to explore in specially designed studies.

Postoperative management

In Study I we examined the general compliance to guidelines with focus on differences between hospital categories. Based on randomised controlled trials, which show a relative reduction in mortality rate of approximately 30% [40], the guidelines recommend postoperative adjuvant chemotherapy for patients younger than 75 years of age operated on for colon cancer stage III. An excellent example of how recommendations in the guidelines improved the information to the clinicians handling this group of patients, and how further scientific evidence can influence clinical practice, is the finding that the frequency of patients given adjuvant chemotherapy increased from 62% in 1997 to 84% in 2000.

The postoperative management of the patients is also influenced by the pathology report. In Study III we investigated the variability in compliance to guidelines and in the quality of the pathology report between different pathology departments. The postoperative management and further treatment of the patient are highly dependent on the classification of the tumour stage.
Only 19% of the examinations fulfilled the recommendations that a minimum of 12 nodes examined and that the number examined should be stated. However, as a result of conferences between surgeons, pathologists and oncologists, where these data were presented and discussed, an improvement was seen. The relative numbers of reports in which the number of nodes examined was stated increased (20% in 1997 and 90% in 2002), as also did the number of nodes examined (median 6 in 1997 and 9 in 2002). Another result of this study, and an example of how guidelines can be used in clinical practice, is the introduction of a common, standardised pathology report protocol for the health care region. The fact that the quality of the pathology report considerably influences the chance of surviving a colorectal cancer, points to this step as an important improvement project. Lack of resources is a common explanation for the deficient compliance to guidelines for specimen examination and description. Our data reveal that a distribution of resources aimed at achieving an acceptable quality is cost-effective for the health care system.

**Survival**

Survival is the ultimate endpoint in most studies. Colorectal cancer survival has increased since the beginning of 1960, reaching a 5-year survival rate of above 50% in the late 1990s [34]. Tumour stage is the most important prognostic factor overall. However, the present thesis has entered more deeply into other specific factors that influence survival.

The reduced survival rate in patients undergoing emergency surgery for colon cancer (Study II) is mainly a result of a more severe tumour stage, as previously pointed out by others [81]. In contrast to Smothers *et al.* [82], we found a stage specific, lower survival rate after emergency surgery, even after correction for a higher postoperative mortality. The explanation for this is an interesting challenge, which is still not sufficiently studied, but there is a high potential for improvement.

Correct tumour staging influences the further treatment and outcome in colon cancer patients. The importance of this was shown in Study III as a difference in survival rate among patients operated on for colon cancer stage II depending on whether fewer or more than 12 mesenteric lymph nodes were examined. The observed improvement in the quality of pathology reports during the study period is an excellent example of how quality registers, linked to clinical guidelines, can be used in quality improvement work. Although an influence of this improvement on the survival rate has not yet been demonstrated, a longer follow-up time will probably reveal this effect.

As many studies are focused on improvement of the survival rate, one important task is to identify different key variables for improvement. Is a concentration to fewer units the right way [46], or the implementation of structured training programmes [83, 84] and workshops for standardisation of surgical techniques [31, 56] and improvement of technical skills? In these
efforts it is also important to incorporate discussions and calculations of costs that will be influenced by the changes.

**Health economy**

The cost explosion in public health systems in recent years [85] has resulted in continuously increasing demands on data for calculating effects on health economy. With the introduction of case costing systems and the CPP registry, analyses of economic structures and comparisons between hospitals and units are now possible [62], as well as different ways of structuring colorectal cancer care. With linkages to population-based quality registers this offers large possibilities for improvement and a more effective distribution of health care resources. The higher relative cost for patients requiring emergency surgery (*Study II*) is mainly explained by a longer duration of hospital stay. However, factors related to an increased frequency of complications and reoperations, such as x-ray and laboratory costs, which are not registered today, are important issues for improvement [86].

**Future potential aspects**

In an attempt to reduce the number of patients with manifest colorectal cancer, and to improve the survival rate among those diagnosed, we have to deepen our knowledge in epidemiology, screening, surgical techniques, perioperative handling of the patient, and adjuvant treatment. The improved survival rate seen in the last decades is a result of many different factors and a source of inspiration for further studies.

The stage specific, lower survival rate among patients undergoing emergency surgery for colon cancer is an interesting field for new studies. Is there a difference in tumour biology between those having elective surgery and the emergency cases? Is the surgical technique suboptimal in the emergency situation? Do surgeons not sufficiently trained in colorectal surgery perform the emergency procedures? Is the decreased survival rate in patients operated on for colon cancer stage II, when too few lymph nodes are examined, not only due to inadequate pathology reports but also to the surgical technique? To clarify this we need to analyse the education of surgeons, and the influence of workshops for surgical skills, at an individual level.

Case-costing data and analyses of health economy are demanded in modern health care systems. Surgical complications increase costs, but there are few studies of more specific questions in this field. What specific issues influence the cost of anastomotic leakage after rectal cancer surgery? What steps to avoid adverse events in the health care process of colorectal cancer are cost-effective? These are all important issues for future studies.
Conclusions

In the light of its prevalence, even small changes in trends, treatment and outcome of colorectal cancer are important on a population basis. An important reason for analysing data and results in unselected population-based materials is to form a basis for quality assurance programmes. The economic aspect is also important in all modern planning of health care. To close the gap between evidence-based guidelines produced in consensus, and clinical practice linked to case-costing data, must be the ultimate goal. In the multifactorial structure constituting modern health care, the analysis of one given endpoint alone, often long-term survival, is not specific enough to form a basis for quality control. We found a variation in compliance to guidelines between hospital categories, partly due to local traditions and resources. The duration of hospital stay also differed between different hospital categories, and for each surgical procedure there was a correlation between hospital stay and cost.

Emergency surgery for colon cancer is frequent and associated with an increased mortality rate, both postoperative and measured as stage specific long-term survival. Co-morbidity is an important factor for the surgical outcome. Factors related to the stage specific decrease in survival rate have not been identified and this requires further studies. Emergency surgery entails increased cost, the most important determinant of which is the longer duration of hospital stay following emergency procedures. Introduction of screening programmes for colorectal cancer may be one possible way to decrease the frequency of emergency interventions.

Correct staging of patients operated on for colon cancer is decisive for further oncological treatment and for prediction of long-term survival. A prerequisite for the oncologist’s decision about postoperative treatment is a valid report from the pathologist after examination of the resected specimen. A decreased survival rate is seen among patients with tumours of stage II when fewer than 12 nodes are examined, and in those with stage III an Index of Metastasis can be used as a prognostic factor. The number of nodes examined is a measure of the quality of the pathologist’s examination and can be used as an instrument in quality control discussions.

Anastomotic leakage is one of the most serious complications after rectal cancer surgery. No decrease in the incidence has been shown, despite the improvement of the surgical technique for rectal cancer. In concordance with earlier discussions, we used the rectal cancer quality register to achieve clinical improvement by systematic measures focusing on anastomotic leakage. Unfortunately, our hypothesis that the decision-making during the perioperative course includes factors important for the incidence of anastomo-
tic leakage could not be confirmed. Further studies of factors related to the individual surgeon and to the surgical technique are required.
Inledning
Cancer i tjocktarm och ändtarm, kolorektal cancer, är en av de vanligaste cancerformerna i världen men med en stor geografisk variation. Den lägsta förekomsten ses i Afrikanska länder och i södra Asien med ca 1 insjuknad årligen per 100 000 invånare, medan kolorektal cancer är vanligast förekommande i Nordamerika och Västeuropa, över 50 på 100 000 invånare och år. Dessa skillnader förefaller inte bara bero på genetiska faktorer, eftersom i folkgrupper som flyttar från områden med låg, till områden med hög förekomst, ökar insjuknandet i kolorektal cancer. Man har sett i epidemiologiska studier att kosten sannolikt spelar en viktig roll i detta. Högt intag av fett verkar öka risken, samtidigt som lågt fiberintag ser ut att öka risken ytterligare.

I Sverige är kolrektal cancer den tredje vanligaste cancerformen, efter bröst- och prostatacancer, med över 5 000 nya fall per år. Kolorektal cancer drabbar framför allt äldre, medianåldern vid insjuknande är ca 75 år, och före 40 års ålder är cancerformen relativt ovanlig. De flesta av de som insjuknar i kolorektal cancer är sporadiska fall, men ärftliga former finns och familjer med ökad risk finns beskrivna. Andelen ärftliga former varierar troligen mellan olika regioner men utgör ca 1-15% av all kolorektal cancer. Familjär adenomatous polyposis (FAP) och Heriditaty non-polyposis colorectal cancer syndrom (HNPCC) är två exempel på ärftliga cancerformer. Dessa uppträder vanligtvis tidigare än de sporadiska cancerformerna, oftast kring 40-årsåldern, men ibland även tidigare.

Diagnos
De första symtomen vid kolorektal cancer är oftast ospecifika, med t.ex. diffus smärta i buken eller ändrade avföringsvanor där blod och slem kan förekomma. Trötthet pga. järnbrist, anemi, är ett vanligt symtom. En utredning med rektoskop och kolonröntgen eller koloskopi kan då ge diagnosen. Innan beslut om vilken behandling patienten ska ha, görs även undersökningar av bl.a. lever och lungor, vanliga med skiktröntgen, CT, eller ultraljud. I knappt 25% av fallen insjuknar patienten akut med mer dramatiska symtom så som tarmvred, ileus, tarmperforation eller kraftig blödning, och måste då opereras akut.
**Behandling**

Den huvudsakliga behandlingen av kolorektal cancer är operation. Oftast kan den del av tarmen där tumören sitter opereras bort, samtidigt som man tar med omkringliggande vävnad med blodkärl, lymfbanor och lymfkörtlar, och tarmändarna kopplas ihop, anastomoseras, för att återställa kontinuiteten. Patienter med cancer i ändtarmen, rektalcancer, får oftast strålbehandling före operationen, ibland i kombination med cytotokatika, för att minska risken för återfallet av cancer. Till patienter opererade för cancer i tjocktarmen, koloncancer, ges ibland tilläggssbehandling med cytotokatika efter operationen, beroende på tumörstadium. De patienter som redan när diagnosen ställs har en spridning, metastasering, av sin cancer, oftast till levern, ibland till lungorna, behandlas fr.a. med cytotokatika och ibland med operation av enstaka levermetastaser.

**Stadium och överlevnad**


Den klart viktigaste prognostiska faktorn vid kolorektal cancer är tumörstadium. Överlevnad har tidigare varit något lägre för rektalcancer, och är så fortfarande i övriga världen, men har de senaste 10 åren i Sverige kommit ikapp den för koloncancer. 5-årsöverlevnaden har för rektalcancer ökat från 31% i början på 60-talet, till 58% i slutet på 90-talet. Motsvarande förändring för koloncancer är från 40% till 57%. Fr.a. är det den ovan beskrivna utvecklingen av förbättrad kirurgi och tilläggssbehandling med strålning och cytotokatika som är orsak till den positiva utvecklingen.

**Vårdprogram och kvalitetsregister**

Under senare år har nationella och regionala kvalitetsregister för kolorektal cancer vuxit fram och flera internationella och svenska studier har visat förbättrad långtidsöverlevnad i takt med förbättrade behandlingsrutiner. Samtidigt som kostnaderna i vården växer, ökar också behovet av system för att kunna mäta och jämföra kostnader mellan olika enheter. 1998 startade i
Landstingsförbundets regi ett nationellt projekt kallat KPP-projektet, Kostnad Per Patient. Syftet var att utveckla ett beräkningssystem där kostnaden för hälso- och sjukvård knyts till den enskilda vårdkontakten och göra det möjligt att följa upp sjukvårdens prestationer och kostnader, samt att jämföra medicinsk praxis i olika sjukvårdsmiljöer.


**Delarbete 1**


Typ av utredning före operation varierade beroende på sjukhuskategori och förändrades under studietiden. Andelen röntgen av tjocktarmen minskade kraftigt samtidigt som andelen koloskopier ökade. Andelen patienter som erhöjd tilläggsbehandling med cytostatika, av de som opererats för koloncancer stadium III, 75 år och yngre, ökade från 62% till 84%. Detta är ett utmärkt exempel på hur rekommendationer i vårdprogrammet, förbättrat information till behandlande läkare och resultat från vetenskapliga studier kan påverka den kliniska handläggningen av patientgrupper.

Kostnadsanalyser visade generellt att operation av rektalcancer var dyrare än operation av koloncancer. Vårdtiden var den faktor som påverkade kostnaden mest, beräknat på individnivå.
Delarbete 2
I delarbete 2 använde vi data från koloncancerregistret 1997-2001 (3259 patienter) för att identifiera riskfaktorer och beskriva resultatet efter akutope-
ration. Vi ville även värdera hur akutooperation påverkar kostnaden.
Vi fann att närmare 25% av de patienter som opererades för koloncancer opererades akut. De akutopererade patienterna hade generellt ett mer avance-
rat tumörstadium än de som opererades planerat, elektivt. Andelen patienter
som avled inom 30 dager efter operation, postoperativ mortalitet, var högre
för de akutopererade. Dessutom fann vi en sämre långtidsöverlevnad för de
akutopererade patienterna, även efter korrigerande för postoperativ mortalitet
och tumörstadium. 5-årsöverlevnad vid stadium III var 37% för akut jämfört
med 49% för elektivt opererade. Ytterligare studier krävs för att kunna klar-
lägga orsaker till denna skillnad. Vårdkostnaden för akutopererade patienter
var högre än för elektivt opererade, och även här var vårdtiden den starkast
drivande faktorn.

Delarbete 3
Korrekt stadieindelning efter koloncancerkirurgi är avgörande för fortsatt
omhändertagande av patienten och för överlevnaden. För korrekt stadiein-
delning krävs en noggrann undersökning av operationspreparatet och be-
dömning av ev. förekomst av lymfkörtelmetastaser. Syftet med delarbete 3
var att identifiera ett möjligt samband mellan antal undersökta lymfkörtlar
och överlevnad, samt mellan antal körtlar med metastas och överlevnad.
Som ett kvalitetsmått ville vi också jämföra de olika patologklinikerna i re-
gionen och deras följsamhet mot vårdprogrammet. Data från koloncancerre-
gistret 1997-2002 (3735 patienter) analyserades.
Vi fann att i endast 64% av patologens rapporter, PAD-svar, fanns antal
undersökta lymfkörtlar angivet. Antal undersökta körtlar var i median 8. För
stadium I-III uppfyllde 20% av PAD-svaren vårdsprogrammets rekommenda-
tion om minst 12 undersökta körtlar. Andelen stadium II (inga körtelmetasta-
sen) minskade och andelen stadium III (med körtelmetastaser) ökade då fler
körtlar undersöktes. Vi fann en sämre överlevnad för patienter klassificerade
som stadium II då färre än 12 körtlar undersökts jämfört med 12 eller fler.
Antal undersökta körtlar har även en prognostisk betydelse vid stadium III.
Ett beräknat metastasindex, IM (antal körtlar med metastas/antal undersökta
körtlar), visade sig vara en starkare prognostisk faktor än den indelning som
används idag, N1 (1-3 körtlar med metastas) och N2 (fler än 3 körtlar med
metastas).

Delarbete 4
Läckage i tarmens hopskarvning, anastomos, är den mest allvarliga kompli-
kationen efter operation av rektalcancer. Trots den förbättring av kirurgisk
teknik vid rektalcancerkirurgi som skett under senare år, med minskad andel
tumöråterfall och förbättrad överlevnad, har andelen anastomosläckage inte
minskat. Ungefär 10% av de patienter som opereras med borttagande av
ändtarm, med tumör, och en hopkoppling av tarmändarna, anastomos, (s.k.
låg främre resektion, LAR) drabbas av anastomosläckage som många gånger
leder till omoperationer, ökad sjuklighet och även ökad dödlighet. Riskfakto-
rer för anastomosläckage har i flera studier visats vara fr.a. manligt kön och
låg anastomos. Syftet med delarbete 4 var att identifiera andra riskfaktorer
än de redan kända, faktorer som är möjliga att påverka och förbättra.

Från rektalcancerregistret i Uppsala/Örebroregionen och Sydöstra regio-
nen identifierades alla patienter som opererats med LAR under åren 1995-
2000 och som drabbats av anastomosläckage (134 patienter). Till varje "fall"
matchades slumpmässigt 2 kontroller av de som opererats med LAR men ej
fått anastomosläckage. Efter en noggrann genomgång av samtliga patienters
journaler (402 patienter) och analys av insamlade data kunde vi konstatera
att manligt kön, strålbehandling före operation, låg anastomos, avvikande
händelse under operation, stor blödning under operation och lång operations-
tid var faktorer som ökade risken för anastomosläckage. Det förefaller som
om faktorer relaterade till den enskilde kirurgen kan ha betydelse och ytterli-
gare studier av detta behövs.

Sammanfattning
Populationsbaserade kvalitetsregister och hälsoekonomiska register, t.ex.
KPP-registret, kopplade till kliniska vårdprogram är en utmärkt bas för kva-
litetsförbättrande projekt och för beslut angående resursfördelning i hälso-
och sjukvårdsplanering. Det svenska systemet med personnummer ger unika
möjligheter att genomföra epidemiologiska och populationsbaserade studier.

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