# Aspects of survival from colorectal cancer in Denmark

*Lene Hjerrild Iversen*

Correspondence: Department of Surgery P, Aarhus University Hospital, Tage Hansens Gade 2, 8000 Aarhus, Denmark

E-mail: lene.h.iversen@dadlnet.dk

The thesis is based on the following Papers, which will be referred to by their Roman numerals:

I. Iversen LH, Pedersen L, Riis A, Friis S, Laurberg S, Sørensen HT. Population-based study of short- and long-term survival from colorectal cancer in Denmark, 1977-1999. British Journal of Surgery, 2005, 92: 873-880.

II. Iversen LH, Nørgaard M, Jepsen P, Jacobsen J, Christensen MM, Gandrup P, Madsen MR, Laurberg S, Wogelius P, Sørensen HT. Trends in colorectal cancer survival in northern Denmark: 1985-2004. Colorectal Disease, 2007, 9: 210-217.

III. Iversen LH, Pedersen L, Riis A, Friis S, Laurberg S, Sørensen HT. Age and colorectal cancer with focus on the elderly: Trends in relative survival and initial treatment from a Danish population-based study. Diseases of the Colon & Rectum, 2005, 48: 1755-1763.

IV. Iversen LH, Harling H, Laurberg S, Wille-Jørgensen P. Influence of caseload and surgical speciality on outcome following surgery for colorectal cancer: a review of evidence. Part 1: Short-term outcome. Colorectal Disease 2006, 9: 28-37.

V. Iversen LH, Harling H, Laurberg S, Wille-Jørgensen P. Influence of caseload and surgical speciality on outcome following surgery for colorectal cancer: a review of evidence. Part 2: Long-term outcome. Colorectal Disease 2006, 9: 38-46.

VI. Iversen LH, Nørgaard M, Jacobsen J, Laurberg S, Sørensen HT. The impact of comorbidity on survival of Danish colorectal cancer patients from 1995 to 2006 – a population-based cohort study. Diseases of the Colon & Rectum, 2009, 52: 71-78.

VII. Iversen LH, Nielsen H, Pedersen L, Harling H, Laurberg S. Seasonal variation in short-term mortality after surgery for colorectal cancer? Colorectal Disease, 2010, 12(7 Online):e31-6.

VIII. Iversen LH, Bülow S, Christensen IJ, Laurberg S, Harling H. Postoperative medical complications are the main cause of early death after emergency surgery for colon cancer. A nationwide study. British Journal of Surgery, 2008, 95: 1012-1019.

IX. Iversen LH, Kratmann M, Bøje M, Laurberg S. Self-expanding metallic stents as bridge to surgery in obstructing colorectal cancer. British Journal of Surgery, 2011, 98: 275-81.

X. Iversen LH, Antonsen S, Laurberg S, Lautrup MD. Therapeutic delay reduces survival of rectal cancer but not of colon cancer. British Journal of Surgery, 2009, 96: 1183-1189.

## 1. INTRODUCTION

The relative survival from colorectal cancer has improved with time in Western Europe and the United States, although differences persist between the countries (1,2). In the period 1985-1989, the 5-year relative survival from colonic cancer was 47% in Europe and 60% in the United States, and for rectal cancer, it was 43% in Europe and 57% in the United States (3).
The outcome of an illness, including cancer, depends on the biology of the illness, the accuracy and utility of diagnostic tests, the effectiveness of treatment, the patient and structural factors (4). For colorectal cancer, the most important factors for improved outcome are earlier diagnosis and better treatment (2). The geographical differences in survival from colorectal cancer are likely due to variations in patient factors like socioeconomic deprivation (5,6), use of screening and early-detection methods, and the effectiveness of treatment.
Survival from colorectal cancer differs even in the Nordic countries, with the lowest survival figures in Denmark, even if the populations enjoy free access to health care services and are fairly homogenous, also socioeconomically. The inferior survival from colorectal cancer in Denmark was reported more than a decade ago: the age-adjusted 5-year relative survival rates from colon cancer diagnosed in the period 1978-1992 were as follows for men and women, respectively: Finland 46%/47%, Norway 46%/49% and Denmark 37%/41% (7). Mortality in the first year after diagnosis has been shown to be particularly excessive in Denmark (7,8). Like for colorectal cancer, survival rates for many

other cancer sites are also lower in Denmark than in other Western and Nordic countries (1,7,9,10).

This thesis reports survival from colorectal cancer over the past decades among Danish patients and explores different aspects of the inferior short-term and long-term survival. The first chapters describe 'Characteristics' and 'Management of colorectal cancer patients in Denmark over the past decades'. These chapters are followed by a chapter on 'Methods and methodological considerations'. Anticipations, limitations and issues that may influence the author's analyses are emphasized continuously throughout in the chapters preceding the 'Results and discussion'.

## 2. CHARACTERISTICS OF COLORECTAL CANCER IN DENMARK

### 2.1. DEFINITION
Cancer of the colon (colonic cancer) and of the rectum (rectal cancer) is collectively referred to as a single disease called colorectal cancer. The tumour is located in the colon in about two thirds of patients and in the rectum in the remaining third of patients. Since the 1990s, the rectum has been defined as the part of the bowel within 15 cm from the anal verge.
More than 95% of colorectal cancers are adenocarcinomas that arise from the glandular epithelium of the colon or rectum. The remaining 5% of colorectal tumours are carcinoid, malignant melanoma, sarcoma, lymphoma, or squamous cell carcinoma. In this thesis 'colorectal cancer' means adenocarcinomas only.
Issues with potential impact on the analyses: Until the early-mid 1990s, tumours situated in the rectosigmoid junction were classified as rectal cancer. A change in the classification causing the proportion of colonic cancer to rise and the proportion of rectal cancer to decrease should be considered when present-day outcome data are compared. In the period before the classification was changed, the long-term survival from colonic cancer was superior to that from rectal cancer; thus, the change meant that some patients with an "inferior" prognosis were transferred to a group with a better prognosis.

### 2.2. INCIDENCE AND AGE
In Denmark like in many Western populations, colorectal cancer is the third most common form of cancer among men and the second among women. The annual number of new colorectal cancer patients has increased from 3,215 in 1991 (11) to 4,258 in 2009 (12). The life-time risk, i.e., the cumulative incidence, for a Dane to develop colorectal cancer is 5% (13). The age-standardized incidence rates in 2009 are shown in **Table 1**. Since 2000, the incidence of rectal cancer has risen by 12% for men and by 10% for women. A similar rise in incidence has been seen for colonic cancer (men 9%; women 11%) (12).

**Table 1**

**Danish age-standardized incidence rates of colorectal cancer, (No. of patients / 100,000 in 2009) (12)**

| Tumour site | Men | Women |
|---|---|---|
| Colonic cancer | 53 | 44 |
| Rectal cancer | 33 | 17 |

The incidence of these cancers rises with age. In Denmark, the median age of patients with colonic cancer is 72 years and with rectal cancer 68 years (14). The proportion of elderly patients aged >75 years rose from 37% in the period 1977-1982 to 42% in the period 1995-1999 (III).

### 2.3. SYMPTOMS AND PRESENTATION
The most frequent initial symptoms reported by colonic cancer patients are vague symptoms like tiredness because of anaemia, weight loss, nausea, decreased appetite, while some also report change in bowel habits and abdominal pain (15). Rectal cancer patients report rectal bleeding and change in bowel habits as their most frequent symptoms (15). None of the symptoms are predictive of colorectal cancer and they all are ill-defined except rectal bleeding.
The majority of colorectal cancer patients present with symptoms making elective evaluation possible. However, about 14% of colorectal cancer patients, mainly those with colonic cancer, present as surgical emergencies because of bowel obstruction, perforation or severe bleeding. The rate of patients who had emergency surgery fell from 16% in 2001-2004 (16) to 12% in 2008 (17) as further discussed in Section 3.2.1.2.

### 2.4. STAGE
The staging system for colorectal cancer developed by Cuthbert Dukes in 1930 and later revised by him and others (18) is being been used worldwide. Dukes' staging is based only on the pathologic examination of the tumour, i.e., the depth of tumour infiltration into the bowel and any spread to regional lymph nodes. Locally excised tumours cannot be staged, and staging of patients with distant metastases is not possible based on the original Dukes' staging system.
The TNM (Tumour, Node, Metastasis) (19) system has been developed to provide uniformity for staging of all types of cancer. For colorectal cancer, the T-stage indicates the depth of tumour infiltration into the bowel wall, the N-stage the extent of tumour-involved regional lymph nodes and the M-stage the presence of distant metastases or persistence of residual tumour after treatment. The TNM system allows staging of all tumours because it allows the use of the extension 'x' for an unexamined stage. The TNM staging of a tumour may change following for example preoperative neo-adjuvant treatment which can be classified by the prefix 'y' (20). During 2003, surgeons started to report the TNM classification of all colorectal cancers as a part of their reporting to the Danish Colorectal Cancer Group (DCCG) database. As from 2004, physicians have been requested to classify each new cancer disease according to the TNM system upon reporting to the hospital discharge registries. The correlation between Dukes', the TNM and the Union for International Cancer Control (UICC) staging systems is shown in **Table 2**.

**Table 2**

**Staging systems**

| Dukes | TNM | UICC |
|---|---|---|
| A | T1-2N0M0 | I |
| B | T3-4N0M0 | II |
| C | $T_{any}$ N1-2 M0 | III |
| "D" | $T_{any}$ $N_{any}$ M1 | IV |
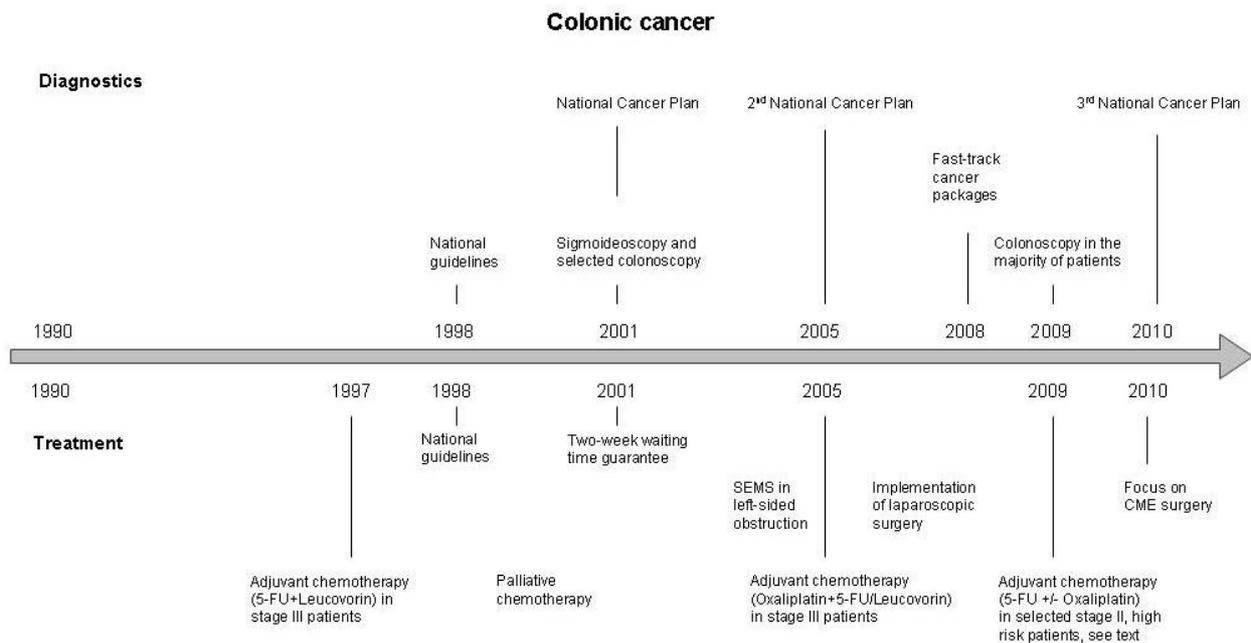
**Colonic cancer**



**Figure 1**
**Flow chart on diagnostics and treatment of colonic cancer in Denmark, 1990s-2010**

A minimal temporal shift in stage distribution has occurred in Denmark over the past 30 years: Despite refinements of diagnostics, see Section 3.1., the proportion of patients with metastatic disease at the time of diagnosis fell gradually from 22% in the period 1977-1982 to 18% in the period 1995-1999 (I) after which this proportion of patients has remained constant at 18% (16). In contrast, the proportion of patients with spread to regional lymph nodes, stage III, has been almost stable during the past 30 years despite the increasing awareness of the clinical impact of detection of positive nodes: such patients have been offered adjuvant chemotherapy since 1997. Adequate N-staging is dependent on lymph node harvest. Since 2004, the DCCG has recommended that at least 12 lymph nodes should be examined in at least 75% of patients after curative resection to ensure proper N-staging (21). The proportion of patients with stage III was 28% in 1977-1982 (I), increased to 31% in 1995-1999 (I) and stabilized at 29% in 2001 (17) and 28% in 2008 (17). Similarly, the proportion of patients with early cancer, stage I, has been about 10% and with stage II about 35% since 2001 (17).

Issues with potential impact on the analyses: The definition of the TNM system has been changed several times which makes comparison of stage and outcome over time troublesome. Even the definition of spread to lymph nodes has changed over time. Correct N-staging and M-staging require a proper search for metastatic disease. Search procedures and practices vary considerably among hospitals. Diagnostics have improved over time, see Section 3.1. The possibilities for diagnosing more patients with metastatic disease, i.e., stage migration, have therefore improved (22). The description of stage in this thesis will therefore rest exclusively on the absence (stage I and II) or the presence of tumour-involved regional lymph nodes (stage III) and the presence of distant metastases (stage IV).

## 3. MANAGEMENT OF COLORECTAL CANCER IN DENMARK DURING THE 1990S–2000S

Denmark had no national guidelines for management of colorectal cancer until 1998 when the Danish Society of Surgery published 'National guidelines for diagnosis and treatment of colorectal cancer' aiming to standardize management of colorectal cancer at all Danish hospitals (23). These guidelines have been updated regularly by the DCCG (24-26). The management of colonic and rectal cancer during the past decades is summarized in flow charts, **Figures 1 and 2**.

### 3.1. DIAGNOSIS AND PREOPERATIVE STAGING
Denmark still has no national screening programme for colorectal cancer. Thus, almost all Danes with colorectal cancer present with symptoms. A screening programme with faecal-occult-blood tests (Hemoccult-II) was undertaken in Funen in 1985-1995 as part of a randomized trial (27). To evaluate the anticipated effect of a planned national screening programme before its implementation, a feasibility study was performed in the counties of Copenhagen and Vejle during August 2005 to December 2006 (28). The participation rate was 67% in the Funen study, but only 48% in the recent feasibility study. Both studies demonstrated the benefit of screening as evidenced by a significantly reduced mortality rate from colorectal cancer (27) and the detection of colorectal cancer at an earlier stage (28). The third National Cancer Plan from November 2010 recommends a national screening programme, but financing of the screening is not in the Budget until 2014.
The diagnostic practices have changed gradually during the 1990s from double-barium enema and rigid proctoscopy to colonoscopy

## Rectal cancer
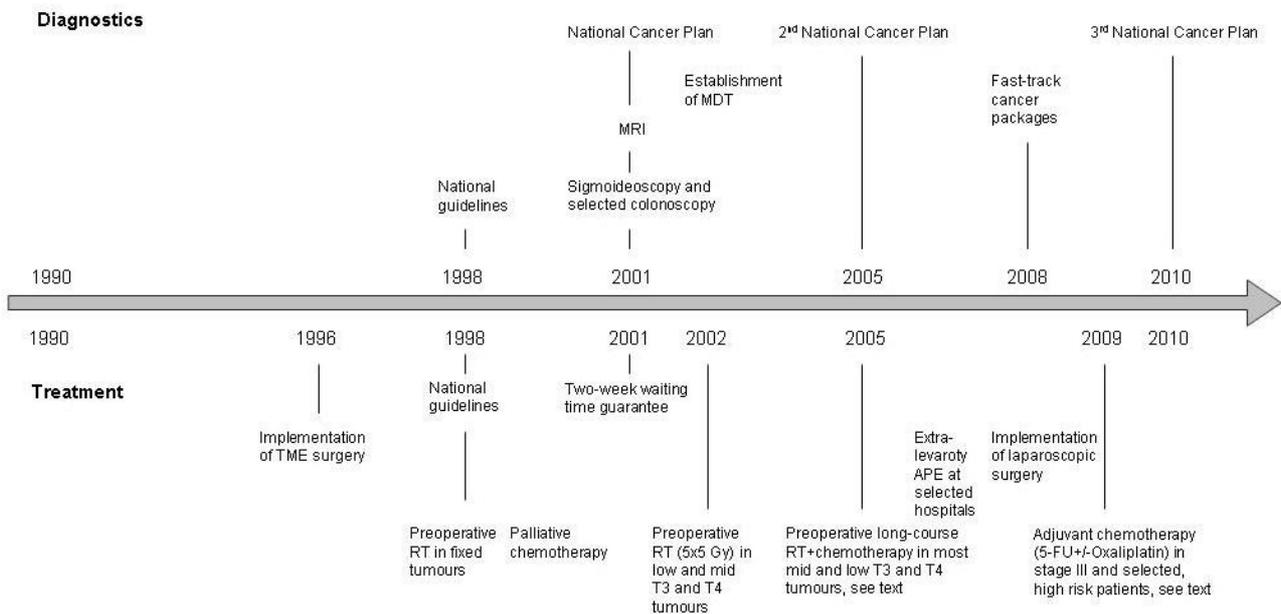


**Figure 2**
**Flow chart on diagnostics and treatment of rectal cancer in Denmark, 1990s–2010**

and sigmoidoscopy. In 2001, the National Board of Health published a Health Technology Assessment recommending a new diagnostic strategy with sigmoidoscopy as the initial investigation in patients above 40 years suspected of colorectal cancer and only colonoscopy in selected cases (29). The national guidelines from 2002 recommended this strategy for the vast majority of patients with defined symptoms suggestive of colorectal cancer (24). However, a PhD study showed that 55% of patients underwent both sigmoidoscopy and colonoscopy (30). In 2009, a Health Technology Assessment recommended colonoscopy as the initial investigation in order to reduce the number of double investigations (31). The diagnostic strategy was accordingly revised in the national guidelines of 2009 with revision in 2010. It now recommends (i) colonoscopy or sigmoidoscopy in patients with change in bowel habits >4 weeks and (ii) colonoscopy in patients with either occult bleeding or rectal bleeding combined with change in bowel habits (26). Gradually, during the 2000s, some patients were being diagnosed by means of computed tomography (CT) colonoscopy.

Preoperative or postoperative staging by use of chest X-ray and ultrasonic liver scan has gradually being replaced by preoperative CT of the thorax and abdomen, partly as a consequence of major advances in non-invasive diagnostic technology. These new techniques may have contributed to some stage migration (22). Preoperative local staging of rectal cancer using magnetic resonance imaging (MRI) of the pelvis was introduced in 1990s and has since about 2001 been implemented on a nationwide basis after which treatment plans of rectal cancer patients have been developed by a multidisciplinary team (MDT). A MDT may consist of radiologists, surgeons, pathologists, oncologists and nurses

(case manager). The establishment of MDT has improved the organisation of treatment of rectal cancer.

### 3.1.1. Diagnostic delay

The clinical pathway, i.e., the pathway from first symptom until treatment, of colorectal cancer includes the time span for patients to react on symptoms and contact the general practitioner, the time span for the general practitioner to interpret the patient's symptoms as potential cancer symptoms and to refer the patient to relevant investigations, and the time span for the hospital to make investigations confirming or rejecting the diagnosis and to perform preoperative staging and initiate treatment. The diagnostic pathway can be categorized into (a) patient delay, (b) delay in primary health care, and (c) delay in secondary health care or hospital delay, **Figure 3**. The sum of delay in primary health care and hospital delay is termed 'provider delay' and the sum of all delays 'total therapeutic delay'.

During the 1990s, the public became increasingly unsatisfied with the waiting time for surgery and in 2001, the Government issued a 2-week waiting time guarantee from diagnosis to treatment. In 2005, the second National Cancer Plan recommended pre-planned, well-structured clinical pathways without unnecessary waiting times for investigations and procedures, i.e., fast-track cancer packages, although they did not become a nationwide reality until 2008. In 2007, the Government stated that cancer should be addressed as an acute condition and patients suspicious of cancer should be investigated within 2 working days. Thus, focus has been on reducing the time span for the hospital to confirm or reject the diagnosis and to initiate treatment.
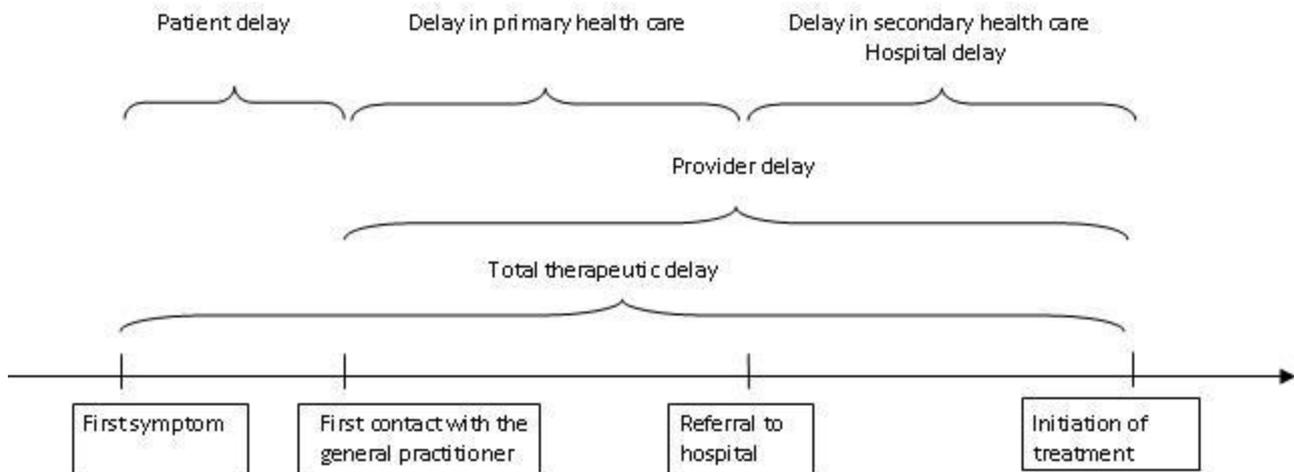
**Figure 3**
**Categorization of delay (modification of (32))**

Anticipations that may influence the analyses: Referral guidelines for suspected colorectal cancer during the 2000s and waiting time guarantee, including fast-track cancer packages, since late 2000s have been instrumental in reducing hospital delay, and time from referral to surgery has decreased by 37% as reported by the DCCG (17).

3.2. TREATMENT WITH CURATIVE INTENT
The mainstay of treatment for colorectal cancer is surgical resection of the tumour-involved bowel segment and its regional lymph nodes. No other treatments have shown to be more efficient with respect to the cure of colorectal cancer. An important parameter of treatment success is the radical resection rate, i.e., the rate at which tumour control is achieved, including macro- and microscopic free resection margins and no distant metastases. Radical surgery was obtained among 23-48% of patients in the period 1977-1982 according to data from the Danish Cancer Registry (III). The DCCG has been reporting the radical resection rate since 2001. The rate rose from 69% in 2001 to 78% in 2008 (17). In other words, although more patients received treatment with curative intention, every fifth to every fourth patient were not cured for their colorectal cancer in the late 2000s.

Anticipations that may influence the analyses: Several factors, non-surgical but with much importance for surgery, have contributed to improve the short-term outcome of treatment for colorectal cancer over the past decades. These factors include advances in anaesthesiologic monitoring and treatment, among others the introduction of less cardio-pulmonary-depressive analgetics, and even before that time, the introduction of perioperative antibiotics and thromboprophylaxis. The beneficial multimodal rehabilitation was not implemented until the late 2000s (33).

### 3.2.1. Surgical treatment of colonic cancer
3.2.1.1. Elective surgery
Standard surgery involves segmental bowel resection with central ligation of supplying arteries, draining veins and lymph vessels, wide mesenteric resection and creation of an anastomosis as

described more than 100 years ago (23). Worldwide, elective surgical treatment of colonic cancer has undergone no dramatic changes over the past century.

Anticipations that may influence the analyses: Some surgical refinement has taken place: (i) Resection of adherent adjacent organs to avoid tumour perforation during dissection has had significant prognostic impact (34,35). (ii) The laparoscopic approach was gradually implemented during the 2000s. Randomised trials suggest some improvements in short-term outcome (36) with no negative effect on the oncological outcome (37) from the shift from open to laparoscopic surgery. In 2005, 6% of Danish colorectal cancer patients underwent a complete laparoscopic procedure (16) and this proportion had risen to 31% in 2008 (17). (iii) Recently, focus has shifted to mesenteric resection. Hohenberger has suggested a novel, potentially promising approach that consists of careful and extensive mesenteric resection along the embryological planes with true central ligation of the supplying arteries, draining veins and lymphatic drainage: complete mesocolic excision (CME) with intact visceral fascia coverage of tumour and mecolon (38). Its prognostic impact awaits further investigation. Thus, the surgical technique of colonic cancer is neither clearly defined, nor does it rest on solid evidence.

3.2.1.2. Emergency surgery
The management of patients who present as surgical emergencies because of bowel obstruction, perforation, or severe bleeding is a major surgical challenge. Bowel obstruction is the most frequent condition. Right-sided obstruction has generally been treated with segmental resection and anastomosis. Left-sided obstruction and perforation have previously been managed with segmental resection and colostomy a. m. Hartmann or a diverting stoma only. The strategy later changed to segmental resection and intraoperative colonic lavage and primary anastomosis with or without a temporary loop-ileostomy, i.e., two- or three-stage resection. Another approach is colectomy with or without primary ileo-rectal anastomosis. Some patients with left-sided obstruction are treated with segmental resection and primary anastomosis. None of the surgical strategies mentioned above have proven their superiority (39).

Issues with potential impact on the analyses: Emergency surgery for colorectal cancer has never been defined precisely in Denmark. In England, 'emergency surgery' means surgery carried out within two hours of admission or in conjunction with resuscitation, whereas 'urgent surgery' means surgery carried out within 24 hours of admission. In Denmark, the great majority of emergency surgeries are therefore urgent surgeries according to the English definition. Furthermore, it cannot be ruled out that some patients admitted acutely and having undergone surgery during that hospital stay may have been falsely classified as patients undergoing emergency surgery. In Denmark, the rate of patients undergoing emergency surgery fell from 16% in 2001-2004 to 12% in 2008 (see Section 2.3.), simultaneously with an increase in the use of self-expanding metallic stents in patients with acute bowel obstruction, Section 3.2.1.3. The population of patients who have had emergency surgery has therefore changed during the past decade which has seen a relative rise in the proportion of patients undergoing surgery due to perforation.

3.2.1.3. Self-expanding metallic stents as bridge to surgery
Self-expanding metallic stent (SEMS) insertion for relieving acute bowel obstruction and later surgery in an elective setting, i.e., the use of SEMS as bridge to surgery, was first described by Tejero in 1994 (40). Since the early 2000s, left-sided obstruction has increasingly been relieved with SEMS at selected Danish hospitals. The SEMS approach allows conversion of emergency surgery into elective surgery in the majority of patients. It thus introduces a time window that allows optimal preparation of the patients for surgery, proper preoperative staging and in selected cases neo-adjuvant radio-chemo-therapy. The SEMS modality was adopted rather quickly in Denmark, probably because of the growing number of studies reporting a poor prognosis after emergency colorectal surgery. Another reason for the quick introduction of the SEMS modality is that Danish surgeons by tradition have done most of the endoscopic gastrointestinal procedures and thus have much endoscopic experience. No randomized trials on SEMS versus emergency surgery have yet been completed, and the evidence level for this approach therefore remains low.

Anticipations that may influence the analyses: The SEMS modality is expected to improve at least the short-term outcome in patients with acute bowel obstruction if technical and clinical success can be achieved.

### 3.2.2. Surgical treatment of rectal cancer
In the early 1990s, rectal cancer patients underwent blunt/conventional rectal resection which was accompanied by the creation of an anastomosis, a Hartmann's procedure, or abdominoperineal excision (APE). The local recurrence rate was high. In 1982, Bill Heald introduced his refined total mesorectal excision (TME) technique in which dissection is performed along the embryological planes. This approach leaves fascia recti propria intact on the specimen, which is associated with a lower recurrence rate (41). Some surgeons practised rectal resection in a TME-like fashion in the early 1990s, but the method was not systematically implemented in Denmark until in 1996 following a training course and subsequent supervision by certified TME surgeons. For patients with a high rectal tumour (11-15 cm from the anal verge), partial mesorectal excision (PME) with resection of the mesorectum 5 cm below the tumour has been a surgical possibility. TME/PME has been the standard technique for rectal resection since the late 1990s.

Since the early 2000s, much attention has centred on the poor prognosis in low rectal cancer. The extended posterior perineal approach in APE a.m. T. Holm (referred to as extralevaroty APE) with its wide pelvic floor excision continuing along the outer surfaces of the levator muscles (42) was gradually implemented, starting in 2006, at a single hospital (43), and afterwards, since 2008, more hospitals have followed suit under the supervision of certified surgeons.
A few early-stage rectal cancers have been managed by local excision only.
Since the early/mid 2000s, treatment options in rectal cancer patients have been evaluated preoperatively and have been the joint responsibility of MDTs at a growing number of hospitals.

Anticipations that may influence the analyses: The long-term outcome of rectal cancer is expected to have improved since the late 1990s because the entire organisation of rectal cancer therapy has been optimized after the implementation of TME surgery. Focus has mainly been on optimizing treatment in rectal cancer and not in colonic cancer. However, TME surgery has never been evaluated and compared with conventional rectal resection in a randomized design. The effect of TME alone therefore remains unknown.

### 3.2.3. Neo-adjuvant radio(chemo)therapy
Rectal cancer patients with tumour-involved resection margins have been offered postoperative radiotherapy for several years (23). Patients with fixed tumours have been offered preoperative radiotherapy followed by surgery 4 weeks later since 1998 (23). The recommendations for radiotherapy in patients with resectable tumours, however, have changed greatly during recent decades. In 1979-1985, a Danish randomized study (CRES) evaluated the effect of postoperative radiotherapy (50 Gy/25 fractions) in rectal cancer patients, (Dukes B and C) and found no survival benefit from postoperative radiotherapy (44), but severe long-term complications (45). In 1997, the Swedish Rectal Cancer Trial reported a significant reduction in the local recurrence rate after preoperative short-course radiotherapy (5 x 5 Gy) (46,47). In 2001, the Dutch study, in which TME surgery was implemented in the beginning of the study period, confirmed the beneficial effect of preoperative radiotherapy on local control (48). Preoperative short-course radiotherapy of resectable T3-4 rectal cancer located within 10 cm from the anal verge, followed by surgery within 1 week, was implemented in Denmark in 2002 (24). In a subgroup analysis, the Dutch study showed no effect of 5 x 5 Gy in low rectal tumours and reports on severe adverse events following short-course radiotherapy appeared (49). The DCCG changed its regimen in 2005 (25). From then on, short-course radiotherapy should be administered only in selected cases, i.e., mid (6-10 cm from the anal verge) T3 tumours with a circumferential resection margin >5 mm (as estimated by MRI). For resectable rectal cancer, the new regimen also implied that long-course (~50 Gy/28 fractions) radiotherapy and concomitant chemotherapy followed by surgery at least 6 weeks later should be offered patients with mid T3 tumours with a circumferential resection margin <5 mm (assessed by MRI), patients with mid T4 tumours and patients with low (within 5 cm from the anal verge) T3-4 tumours (50). The guidelines were revised in 2009 after which patients with mid T3 tumours and a circumferential resection margin >5 mm were spared from preoperative radiotherapy (26).

Issues with potential impact on the analyses: The guidelines on radiotherapy have been changed three times since 2002. Revised

treatment regimens are usually implemented gradually after some delay. The effect of the individual radiotherapy regimens is therefore difficult to determine, even if surgeons use the TME technique.

### 3.2.4. Postoperative adjuvant chemotherapy
In 1990, Moertel reported a significantly improved long-term survival among node-positive colonic cancer patients who had received 5-FU and levamisole following radical surgery (51). In Denmark, only few patients, n = 346, with Dukes B and C colonic cancer received 5-FU and levamisole, in a randomised trial (DAK-REKA) from 1992-1996 (52).
Since 1997, all fit node-positive colonic cancer patients have been offered postoperative chemotherapy like 5-FU and leuko-vorin/levamisole. Since the mid 2000s, the regimen has been supplemented with Oxaliplatin because a further survival benefit was observed for this combination of chemotherapeutics (25). Since 2009 and based on international consensus only, 5-FU +/- Oxaliplatin is being offered to selected high-risk stage II colonic cancer patients (T4 tumours, bowel obstruction, tumour-involved vessels or nerves, perforation, poorly differentiated tumours, and <12 lymph nodes detected in the specimen) (26). The duration of these treatment regimens has been reduced from 12 months in the early 1990s to now 6 months.
In rectal cancer, selected high-risk patients have been offered postoperative chemotherapy with 5-FU +/- Oxaliplatin since 2009 (26). High risk is defined as stage III, low tumour differentiation, T4 tumour, tumour-involved vessels or nerves, bowel obstruction, or perforation.

Anticipations that may influence the analyses: Some of the improvement in long-term survival of stage III colonic cancer patients observed since the late 1990s is expected to have been caused by postoperative adjuvant chemotherapy.

### 3.2.5. Treatment of potentially curable local recurrence, distant metastases or peritoneal carcinomatosis
The management of patients with distant metastases or recurrent disease was rather nihilistic in Denmark during the 1990s. During the 2000s, the view changed gradually; thus, a growing number of patients with potentially curable recurrent disease have been offered resection at selected hospitals (26). Further, the treatment of patients with distant metastases has become more aggressive with the introduction of surgery and radiofrequency ablation, for instance, aiming to cure or palliate only (26). Since 2006, it has been possible at a single hospital to offer cytoreductive surgery and hypertherm intraperitoneal chemotherapy (HIPEC) to selected patients with primary or secondary peritoneal carcinomatosis and no distant metastases (53).

Anticipations that may influence the analyses: Long-term survival is expected to have improved in the (late) 2000s in some stage IV patients because of the introduction of the above-mentioned treatment regimens with curative intent.

3.3. TREATMENT FOR PALLIATION
### 3.3.1. Surgery
During the 1990s, most patients with colorectal cancer underwent surgery with the intent to perform tumour resection unless they were known with massive hepatic metastases for instance. After introduction of the beneficial regimen of palliative chemotherapy in the late 1990s, some patients without obstructive

symptoms were able to escape surgery. During the mid 2000s, patients with metastatic disease less frequently underwent surgery, and they most often did so only in case of perforation or obstruction which cannot be managed otherwise. The late 2000s saw the emergence in recent guidelines of a new trend favouring less invasive surgeries such as insertion of a SEMS, performing a laparoscopic stoma only or creating a by-pass in patients with non-curable disease has appeared in the late 2000s (17).

Issues with potential impact on the analyses: The surgical treatment strategies in patients with non-curable disease have changed over time and the survival benefit of the various strategies awaits further investigations.

### 3.3.2. Self-expanding metallic stents as a definitive procedure
In 1991, Dohmoto described successful SEMS insertion in incurable, obstructive rectal cancer (54). SEMS designed for colorectal use was introduced in Denmark in the early 2000s. The SEMS approach made it possible to relieve obstructive symptoms in patients with incurable disease or severe comorbidity.

Issues with potential impact on the analyses: However, it remains to be clarified whether SEMS or surgical resection (both with addition of chemotherapy) is associated with the best outcome. Thus, surgeons advise patients individually in daily practice.

### 3.3.3. Chemotherapy and radiotherapy
The regimen with 5-fluorouracil and folinic acid was implemented in the 1990s because it outperformed other regimens on survival, yielding a median survival of about 12 months (55,56). The regimen became recommended in national guidelines in 2002 (24). Newer agents, like Oxaliplatin or Irinotecan, and biological drugs like Bevacizumab, are now being offered to supply fit patients with further survival benefits and the median survival has gone up to 16-20 months (25,26).
Palliative radiotherapy has been offered for several years in case of pain and bleeding, among others, for instance in incurable rectal cancer or local rectal cancer recurrence (23).
Stereotactic body radiotherapy and radiofrequency ablation are treatment tools that are increasingly being used in the 2000s for liver metastases (26).

Anticipations that may influence the analyses: Palliative chemotherapy has contributed to some improvement of stage IV patients' survival in recent decades.

### 3.3.4. Supportive care
During the 2000s, focus has increasingly centred on the supportive care offered by palliative teams to optimize care and thus prolong the time the patient may stay at home as much as possible.

Anticipations that may influence the analyses: Supportive care improves the quality of life of patients and their families, but probably contributes minimally, if anything at all, to survival.

3.4. THE DANISH HEALTH CARE SYSTEM AND HOSPITAL AND SURGEON CHARACTERISTICS
Public health care in Denmark is free and tax-financed (57). Denmark consisted of 14 counties up until 2007 at which time the counties were dissolved and replaced by five regions. Hospitals have since the local government reform in 1970 been owned by

the counties and, since 2007, by the regions. The regions (previously counties) hire all hospital staff, including physicians. Colorectal cancer patients in Denmark are treated at public hospitals except a very low number of colonic cancer patients in the capital region which have been treated at private hospitals since mid 2000s.

The health care retrenchment seen during the past decades has triggered a general increase in specialization and centralization activities in the Danish hospital sector. In the late 1980s and early 1990s, several small hospitals stopped treating colon cancer, while centralization of the surgical management of rectal cancer began in the late 1990s and early 2000s. Concentration of surgical cancer treatment was one of the proposals in the National Cancer Plan of 2000 (8). A further centralization occurred after the regions replaced the counties in 2007. The decline in the number of hospitals performing surgery for colonic and rectal cancer nationwide in the past decade is depicted in **Table 3** (17,58). Besides that more patients are treated at county and university hospitals, probably fewer surgeons are treating more patients, although the latter is undocumented. As a consequence of the implementation of TME surgery in 1996, fewer surgeons were allowed to perform rectal cancer surgery. Such a priority has not been adopted in colonic cancer.

**Table 3**

**Number of Danish hospitals treating colorectal cancer during 2001-2010**

| Year | Colonic cancer | | Rectal cancer |
|------|------------------|-------------------|----------------|
|      | Elective surgery | Emergency surgery |                |
| 2001 | 50 | 44 | 47 |
| 2005 | 34 | 34 | 32 |
| 2010 | 20 | 20 | 17 |

Until the late 2000s, surgeons could be trained and educated to become specialists in 'General surgery' and the subspecialty 'Surgical gastroenterology' according to criteria issued by the National Board of Health. As from 2006, specialized surgeons with extensive experience in coloproctology or surgeons who have passed a two-year education and training programme may be named 'certified colorectal surgeon'.

In the 1990s, colorectal cancer surgery was generally performed by senior registrars who had not yet achieved specialist status. If necessary, the senior registrars were supervised by consultant surgeons. The 2000s saw a significant rise in the proportion of patients, notably patients with rectal cancer, who underwent surgery performed by specialists in surgical gastroenterology, **Table 4**. However, in 2008, 40% of emergency colonic cancer patients were being treated by general surgeons or non-specialists.

**Table 4**

**Percentage of Danish colorectal cancer patients treated by specialists in surgical gastroenterology during 2001-2008. The remaining patients were treated by general surgeons or non-specialists (17).**

| Year | Colonic surgery | | Rectal cancer |
|------|-----------------|-----------|----------------|
|      | Elective | Emergency |                |
| 2001 | 39 | 28 | 72 |
| 2005 | 64 | 49 | 89 |
| 2008 | 78 | 60 | 94 |

Issues with potential impact on the analyses: Specialists in surgical gastroenterology may be specialists with main interest in upper gastrointestinal surgery. In the early-mid 2000s, specialist status, as registered in the DCCG database, was an uncertain variable because at that time it was not clearly defined that it means the highest status of the operating or the supervising surgeon. No particular importance should be therefore be ascribed to this variable in the assessment of the results of surgery in this period.

**4. AIMS OF THE THESIS**

The overall aim of the present thesis is to explore different aspects of the inferior short-term and long-term survival from colorectal cancer in Denmark over the past decades.

The specific aims were:

1. To describe the overall short-term and long-term survival from colorectal cancer in Denmark over the past decades

2. To evaluate, for short-term and long-term survival,
• the influence of old age
• the impact of comorbidity
• the influence of structural factors like caseload and surgeon speciality
• the benefit of SEMS in patients with acute bowel obstruction

3. Specifically for short-term survival
• to determine prognostic factors of postoperative mortality after emergency surgery for colonic cancer
• to study whether postoperative mortality from colorectal cancer exhibited any seasonal variation

4. Specifically for long-term survival
• to study the impact of therapeutic delay

**5. METHODS AND METHODOLOGICAL CONSIDERATIONS**

5.1. DATA SOURCES
*5.1.1. Central Population Registry*
Since 2 April 1968, the Central Office of Civil Registration has been assigning a unique 10-digit personal identification number to all Danish citizens (59,60). This number codes for age, gender and date of birth and it allows valid linkage of registries. The Civil Registration system also contains information on vital status (alive/dead), date of death and residence.

*5.1.2. Danish Cancer Registry*
The Danish Cancer Registry is a population-based registry containing data on individuals with malignant diseases in Denmark since 1943 (61,62). Until 1987, reporting to the Registry was voluntary. In 1987, reporting became mandatory for all medical doctors. The change from voluntary to mandatory reporting had no material influence on the number of patients reported (62). In 1997, the registry was moved from the Danish Cancer Society to the National Board on Health.

Patients are identified by their 10-digit personal identification number. Data, which are provided by the reporting physician, are

collected prospectively and include diagnosis (classified according to the modified version of the international classification of diseases, 7th revision (ICD-7) until 2004, thereafter ICD-10, but diagnoses from 1978-2003 have been re-classified according to ICD-10), date of diagnosis, method of verification, staging of tumour at the time of diagnosis (local, regional, distant metastases), treatment given within four months of diagnosis (surgery: yes/no; radiotherapy: yes/no; chemotherapy: yes/no; anti-hormone therapy: yes/no), outcome of treatment (radical/palliative), date of death and cause of death. The classification of surgery as radical or palliative is based solely on information provided by the reporting physician. Registration was based on notification forms until 2004. The forms were completed by hospital departments, including departments of pathology and forensic medicine, and practising physicians when a person was diagnosed with cancer; at autopsy; or when changes were made to an initial cancer diagnosis. Since 1 January 2004, all notifications from hospital departments are reported electronically to the National Board of Health via the Danish National Registry of Patients, and since 1 January 2005, all practising physicians also report electronically to the National Board of Health.

Issues with potential impact on the analyses: The Cancer Registry has been shown to have accurate and virtually complete data on cancer patients. Registry completeness and validity reaches 95-98% (62). Records are supplemented by unreported patients captured through annual linkage to the Danish Register of Causes of Death and to the Danish National Registry of Patients. For patients notified by death certificate only, the physician responsible for the death certificate is contacted in order to explain the missing notification to the Cancer Registry at the time of diagnosis. The proportion of patients identified by death certificate only has been less than 1-2% in recent decades (11,12). For patients identified by the Danish National Registry of Patients only, the treating departments are requested to supply a notification form before the patients can be registrered in the Cancer Registry. The entire coding process is supervised by medical doctors.
Before the introduction of electronical reporting and regular data up-dating in 2004, there was considerable, often year-long, delay in data collection. Before 2004, the Registry was thus not an optimal source for analysis of recent trends in survival.

### 5.1.3. Hospital discharge registries and Danish National Registry of Patients
The hospital discharge registries (called the Patient Administrative Systems, PAS) are used by all Danish Regions (counties until 2007) to collect data from hospital admissions. The registries were established in 1977. Their purpose was to (i) provide data for statistical analyses, (ii) monitor utilization, (iii) support the process of planning for the National Board of Health, (iv) monitor the frequency of various diseases and treatment, and (v) facilitate research and quality assurance (63). Since 1995, out-patient activities and visits at emergency rooms at hospitals have also been registered. PAS data are transferred to the Danish National Registry of Patients. The discharge registry data are updated daily.
The dataset includes the personal identification number, dates of admission and discharge, surgical procedure(s) performed (coding done by surgeons responsible for the operation) and up to 20 discharge diagnoses (coding done by physicians). Discharge diagnoses were classified according to the Danish version of the ICD-8 until the end of 1993 and thereafter according to ICD-10 (63). ICD-8 codes used for colorectal cancer are 153 and 154, and ICD-

10 codes are C18-C21. In 2000, the Danish health care authorities introduced a new accounting method based on Diagnosis Related Groups (DRG). The DRG system provides stronger incentives to record concomitant conditions besides the main condition. Surgical procedures are classified according to a Danish version of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (64). The NOMESCO codes became available on 1 January 1996. The codes used in Papers II, VII, VIII to identify patients who had undergone procedures for colorectal cancer are listed in **Appendix 1**.

Issues with potential impact on the analyses: The validity of the registry data has been shown to be high (65,66). Completeness has been reported to be 92% for haematological malignancies (67) and 96% for ovarian cancer (68). Review of medical records and re-coding by independent clinicians has shown agreement in 90% of admissions to surgical departments, but improper coding of surgical procedures in 15% (66).

### 5.1.4. Danish Colorectal Cancer Group database
The Danish Colorectal Cancer Group (DCCG) database is a national clinical database with data on all patients in Denmark with a first-time diagnosis of colorectal adenocarcinoma treated or diagnosed in surgical departments. The database was founded in 1994 by a subgroup of the Danish Surgical Society. The purposes of the database are support efforts aimed: (i) to unify procedures for diagnosis, treatment and follow-up on colorectal cancer, (ii) to improve and assure the quality of treatment of colorectal cancer, (iii) to reach the quality objectives as described by the Danish Surgical Society and the National Board of Health, and (iv) to support and initiate clinical colorectal cancer research.
In 2005, the DCCG became a multidisciplinary cancer group counting radiologists, oncologists, surgeons and pathologists. From 1994 until May 2001, only patients with rectal cancer were included in the database, but since May 2001, all patients with colorectal cancer have been included.
Patients are identified by their 10-digit personal identification number. The data are collected by all surgical departments and are prospectively entered into the database. Data have been retrieved through questionnaires filled in by the patients (height, weight, comorbidity, symptoms, alcohol and tobacco consumption, self-perceived physical fitness and general health), and the surgeons (diagnostics performed, American Society of Anesthesiologists (ASA) score, staging (Dukes' stage and the TNM classification), urgency of surgery (elective or emergency), treatment, postoperative complications occurring within 30 days after surgery, planned follow-up). From 2005 onwards, reporting has been done via the Internet. From 2010 onwards, data are registered by the surgeons only, and collected data include data on delay as well. In 2010, the database was extended to include more detailed data on pathology and oncology reported by pathologists and oncologists, but reporting by the latter has not yet been satisfactory.

Issues with potential impact on the analyses: Data completeness is validated by daily linkage to the Danish National Registry of Patients. The database was also linked to the Danish Cancer Registry in 2009. Patient registration completeness has been close to 95% since 2002 (16). All departments are notified of missing data and logical errors in the questionnaire responses. The database has continuously been developed to prevent illogical data registration, e.g., radical surgery in case of distant metastases, hysterectomy in males, etc. Some 5% of colorectal cancer patients are

not registered in the database because they have not been admitted to a surgical department. Such patients have received palliative support only at medical or oncology departments. Reporting by the patients on comorbidity and life style factors, among others, has been less than 50%. Therefore, it became mandatory in 2010 for the surgeons to undertake such reporting to make data more valid for analysis of case-mix, among others.

The validity of data reported to the database has been assessed on the basis of a random sample of 5% of patient data reported from May 2001 through December 2001, n = 86. Three independent consultant surgeons re-coded the material based on copies of medical records and they achieved a rather good correspondence: inter-rater agreement on patient diagnoses was 84%, treatment 94%, tumour staging 89%, and the postoperative course 90% (69). No other validation has yet been carried out.

The DCCG registry lacks an exact definition of emergency surgery. 'Emergency treatment' is one of two options surgeons have for operative urgency (emergency/elective) when they enter data into the Registry. Emergency surgery is usually performed in case of bowel obstruction, perforation or severe bleeding. It has been shown that the median time from first contact to the hospital until time of emergency surgery is one day (VIII).

A concern regarding the variable 'Specialist status' is discussed in Section 3.4.

## 5.2. STATISTICAL ANALYSES

### 5.2.1. Survival analyses

Mortality and survival terms are defined in the present thesis as follows:

30-day mortality is mortality from all causes of death within 30 days of surgery, i.e., a postoperative mortality estimate.

In-hospital mortality is mortality from all causes of death during the hospital stay after surgery.

Observed all-cause survival is an estimate of the probability of surviving all causes of death.

Crude survival and overall survival are synonymous terms covering observed all-cause survival.

Relative survival estimates express ratios of observed survival, from all causes of death, of a cohort of cancer patients to the survival that would have been expected if these patients had had the same age- and gender-specific survival as the general population. In other words, relative survival measures the excess mortality associated with the cancer diagnosis and its treatment (70).

Stage-specific survival is all-cause survival calculated for the specific stage in question.

Cancer-specific survival means survival from cancer in the absence of other causes of death. Calculation of cancer-specific survival requires proper specification of the cause of death.

All-cause survival curves for specified periods were constructed and product limit estimates of 1-year and 5-year survival were obtained using the Kaplan-Meier method.

To calculate expected survival in the general population to be used for calculating relative survival, 10 randomly chosen population controls were sampled for each patient from the Central Population Registry. Controls were matched on gender and age (month and year of birth) and should be alive and free of colorectal cancer.This approach made it possible to accurately estimate expected survival per one-year period in the general population in contrast to the per 10-year period that would be necessary if national life tables had been used. The reduction of these periods from 10 years to one year is especially important when calculating survival for old patients. The traditional 'cohort analysis' was

used. In the calculation of the 5-year relative survival, we therefore excluded those diagnosed so recently that they could not be followed for 5 years.

Issues with potential impact on the analyses: The growth in life expectancy, notably among the 70-90-year-olds, is not taken into consideration in the calculation of the crude survival (71). Thus, any survival improvement in this age group may be partly attributable to increased life expectancy in the general population.

The approach of sampling population controls for calculation of relative survival do not take into consideration potential confounders like comorbidity, alcohol and tobacco consumption, obesity and socioeconomic status, among others. An uneven distribution of these factors among colorectal cancer patients and population controls may therefore be present. Some interaction between comorbidity and colorecal cancer does exist: diabetic patients, for instance, have an increased risk of colorecal cancer (72).

Stage-specific survival was not estimated in the present analyses because some stage-migration may have occurred over the past decades. This would translate into an improved stage-specific survival, but it would have no effect on overall survival. The advantage of stage-specific survival is that the differences in survival attributable to a change in stage distribution disappear in comparison of survival over time or between countries. A disadvantage is that the staging classification systems are not consistent.

### 5.2.1.1. Considerations when comparing survival statistics between countries

The reasons for differences in survival between countries are rooted in multiple factors related to (i) registration and analysis like quality and completeness of data in cancer registries, statistical methods for calculating survival, among others; (ii) patients like age, stage, comorbidity, socioeconomic status, race, among others; (iii) treatment like availability and quality of diagnostics, efficacy of treatment, among others; and (iv) structures like access to health care, among others. The current lack of reliable and consistent information on patient factors such as stage and comorbidity between countries hinders a thorough investigation of survival differences.

Survival statistics are affected by variations in registration and quality of data in the cancer registries. The completeness of ascertainment in registries varies considerably among countries (73). Scandinavian cancer registries are known to have almost complete cancer ascertainment, close to 100%, with nationwide coverage. In England, the completeness is much lower, 86-93% (74). Incomplete ascertainment is often due to missing of long-term survivors, wherefore incompleteness tends to bias results towards inferior survival (74), although the opposite may also be observed.

Data collection and cancer registation coverage vary even among the Nordic cancer registries. The Swedish Cancer Registry does not link its data with death certificates and thus does not includes all patients with late-stage disease and expected short life expectancy who tend to bias the results towards better survival. In most survival analyses, patients identified by death certificates only are excluded because such patients have no date of cancer diagnosis. The proportion of death-certicate-only patients varies among the cancer registries with low proportions of such patients in the Denmark and Finland, for instance, and higher proportions in the English registries. A high proportion of such patients also tends to bias the results towards improved survival (74). If the

proportion of death-certicate-only patients decreases over time, survival will be biased towards worse survival.

Data registration problems have been reported to occur in England (75). The English cancer registries are supplemented with the hospital admission data, but the latter do not distinguish explicitly between the date of diagnosis and later events like recurrence. Such incorrect allocation of dates of diagnosis also introduces a bias towards inferior survival estimates (75).

Life expectancy differs even among the Nordic countries with the highest life expectancy in Iceland (81.8 years) and Sweden (80.9 years) and the lowest in Denmark (78.3 years) (76). Certainly, such differences contribute to variations in survival when crude survival rates are compared.

It would be more appropriate to compare survival rates between countries by means of the relative survival method because this approach, as opposed to the use of crude survival would largely ignore differences in general health status. However, the effect of any interaction between general health status and indications for and tolerance of treatments is not taken into account with either method (77). Thus, comparison between countries where populations differ in terms of degree of obesity and alcohol and tobacca consumption patterns, among others, may produce different survival figures because of interaction between these parameters. The use of different statistical methods may contribute to survival differences between countries and registries (78). An example is age-standardized survival: most registries age-standardize to the age distribution of their own country. However, age distributions differ across countries. To facilitate comparison of survival across countries and analyses of the reasons for these variations, complete dataset with comparable items and standardized data from the individual countries are required. Such requirements are seldom met, but efforts to this end have been made with the establishment of the NORDCAN database which is a database hosting comparable data on cancer incidence and mortality from the national cancer registries of the Nordic countries (79). The free health care systems in the Nordic countries exclude access to health care as a confounder in the database.

In comparison of rates of mortality from colorectal cancer, it is important to correlate the mortality rate with the resection rate or the rate of any surgical intervention. Patients who do not undergo surgery undoubtedly do not contribute to 30-day postoperative mortality. This issue is especially important in countries like Denmark with an almost complete ascertainment in administrative and clinical registries. Further, a low resection rate may be a reflection of only unfavourable stage distribution.

Several other factors are known to influence cancer survival and should be considered when survival is compared across countries. Survival is calculated as the number of cancer patients who have survived in a given period divided by the number of patients diagnosed with cancer. In other words, it is correlated with the incidence and with mortality rates, both of which may vary considerably between countries. For example, if mortality decreases because of better treatment, the number of survivors will increase and survival will improve. If the incidence increases because of the introduction of early detection methods, the number of cancer patients will increase and survival will improve even though mortality may remain stable. This can be seen if early detection methods result in (i) diagnosis before the cancer becomes clinically evident, which will induce longer survival, i.e., lead-time bias; or (ii) diagnosis of slowly progressing, indolent cancers, which would probably never be life-treating and thus not affect mortality, i.e., length-time bias (80). Differential use of screening programmes for prostate cancer and associated sub-

stantial difference in incidence is a classical example of major variations in survival between countries despite their similarity in efficacy of treatment (81). In colorectal cancer, screening programmes will similarly increase the (early-stage) incidence and survival, but survival will also increase because efficacy of treatment is stage-specific. Further, screening programmes for colorecal cancer will reduce the incidence of colorectal adenomas, i.e., precursors of cancer. Thus, the incidence may decline over time. Differential use and intensity of screening programmes therefore contributes heavily to survival variations between countries. For instance, the 5-year relative survival from colorectal cancer in the United States has been higher than in Europe because of the widespread use of screening programmes (82).

### 5.2.2. Measurement of comorbidity

In the present thesis, comorbidity is defined as the co-existence of diseases other than colorectal cancer and should be distinguished from functional status.

Functional status or performance status are terms used to denote a measure of a patient's ability to perform daily activities or other tasks, i.e., the terms are used as a proxy for general health. Several approaches have been developed to measure or quantify comorbidity: counts of conditions, analysis of specific conditions and comorbidity indices. The Charlson Comorbidity Index, based on for instance IDC-10 codes, was used in Papers VI and X. The index was developed in the 1980s in a cohort of 559 medical patients and tested for its ability to predict the risk of death from comorbid disease in a second cohort of 685 breast cancer patients during a 10-year follow-up period (83). The Index includes 19 disease categories, each of which are weighted from one to six according to its relative risk of death within one year and then added to form a total score, **Appendix 2**. Thus, the score combines the number and seriousness of comorbid diseases into a single numeric score. To calculate the Charlson Comorbidity Index, we retrieved discharge diagnoses from hospitalizations documented in nationwide hospital discharge registries during a 10-year period prior to the admission for colorectal cancer. Cancer diagnoses made within 60 days before the colorectal cancer diagnosis were excluded from the calculations in order to eliminate possible cancer-related diagnoses. The Charlson Comorbidity Index scores were categorized into three groups: no (score 0), moderate (score 1-2) and severe (score 3+) morbidity.

The ASA proposed a physical status classification of preoperative patients for anaesthetic risk assessment in 1963 (84). The ASA score is commonly used in daily practice by surgeons and anaesthesiologists and it is simple to use. However, it is not exactly defined and thus influenced by inter-observer variation. The ASA score is a surrogate for comorbidity as it does not measure comorbidity in itself, rather the severity of any comorbidity. The ASA score is graded as follows: ASA I means a normal healthy person, ASA II a patient with mild systemic disease, ASA III a patient with severe systemic disease, ASA IV a patient with severe systemic disease that is a constant threat to life, and ASA V a moribund patient who is not expected to survive with or without the operation.

Issues with potential impact on the analyses: During the past two decades, the Charlson Comorbidity Index has been adapted for use with hospital discharge data in ICD-based databases and it has become a widely used, valid and reliable tool for assessing the impact of comorbidities on mortality in many different cancer groups (85-91). It validly predicts mortality within few weeks to 10 years in various conditions, including after cancer surgery

(83,92). The Index is not comprehensive in its adjustment for comorbidity and it has a tendency to underscore comorbidity because it is limited to 19 conditions. Patients with the same Charlson Comorbidity score may have different outcomes because conditions like congestive heart failure may be associated with higher mortality than conditions like connective tissue diseases. Different conditions may also impact the outcome differently depending on the primary condition being investigated, for example congestive heart failure may have a higher impact in rectal cancer than in breast cancer in the postoperative course; but also depending on the outcome being measured, for instance the impact of diabetes mellitus on postoperative morbidity and long-term survival may differ.

Other comorbidity indexes have been developed for health services research deploying administrative data. The performance of four claims-based comorbidity indices (Elixhauser's set of 30 condition indicators, Klabunde's outpatient and inpatient indices weighted for colorectal cancer patients, Diagnostic Cost Groups, and the Adjusted Clinical Group System) has been compared in a cohort study including 5,777 stage III colonic cancer patients (93). Although some of the comorbidity indices demonstrated minor advantages over the others, each was fairly robust in predicting non-cancer death. Further, the ability of the Charlson Comorbidity Index, the Adult Comorbidity Evaluation-27 and the National Institute on Aging and National Cancer Institute Comorbidity Index to predict overall and cancer-specific mortality was compared in 496 colonic cancer patients. The results were similar across the comorbidity instruments (94). No single comorbidity index has outperformed the Charlson Comorbidity Index in predicting mortality among cancer patients.

The study of temporal patterns of comorbidity levels requires that the registration of comorbid diseases is homogenous over time. However, in 2000 the Danish health care authorities introduced the DRG system as a new accounting method which provided economic incentives to record conditions correctly. Such more accurate coding practice may contribute to some "comorbidity score-migration" over time and, as expected, it improved comorbidity-specific survival.

Incomplete registration of comorbid diseases in the hospital discharge registries would result in underestimation of the Charlson Comorbidity Index. On the other hand, one may rely on the diagnoses retrieved from the hospital discharge registries used for calculation of the Index, although such a validation has not yet been performed in Denmark.

### 5.2.3. Seasonal variation
To study the seasonal variation in short-term mortality, we calculated the monthly mortality rate 30 days after surgery with associated 95% confidence intervals (CI) stratified by tumour site (colon/rectum), urgency of surgery for colon cancer (elective/emergency) and ASA score (I /II/≥III). Assuming that the monthly variation demonstrates a single annual cycle with a single peak and a single trough during a calendar year, i.e., a sinusoidal form, a fitted curve of the monthly mortality rates was constructed using a periodic regression model. The peak-to-trough ratio, i.e., the estimated mortality rate in the month of peak relative to the estimated mortality rate in the month of trough, was calculated from the fitted curve. The ratio of peak-to-trough occurrence is an estimate of the relative, monthly mortality risk. If there was no monthly variation, there would be unity and it would increases above one with increasing intensity of seasonality.

## 6. RESULTS AND DISCUSSION

### 6.1. SHORT-TERM SURVIVAL FROM COLORECTAL CANCER
#### 6.1.1. Overall
Thirty-day relative survival: From the late 1970s to the late 1990s, the 30-day relative survival, as measured from time of diagnosis, of colonic and rectal cancer improved by 4% with only marginal gender differences (I). For colonic cancer, the 30-day relative survival rose from 86% in 1977-1982 to 90% in 1995-1999, and for rectal cancer from 90% to 94%. Included in this outcome measure is patients diagnosed with late-stage disease and thus an expected short life expectancy. During the same time period, the 6-month relative survival improved by 8% from 70% to 78% (I). The survival rates for rectal cancer were 5-8% higher than for colonic cancer, with a declining difference over time.

Thus, an overall 8% improvement within the first half year had occurred, which is probably attributable to the general advances in anaesthesia and better peri-operative care.

Postoperative mortality: A more conventional measure of short-term outcome is the postoperative mortality rate as measured by the 30-day mortality or in-hospital mortality. However, most publications quoting 30-day mortality figures are single-centre series and only very few are nationwide population-based studies (17,95-99) (II). It is well-established that some of the determinants of 30-day mortality are age, ASA score, comorbidity, outcome of surgery and urgency of surgery. However, a number of publications (100-109) have pointed to an abundance of other determinants both preoperative factors like serum albumin level, ascites; and intra-operative adverse events and postoperative complications like cardiac arrest, myocardial infarction, failure to wean, systemic sepsis, cerebrovascular accident, renal insufficiency or failure, anastomotic leakage and male gender, among others.

The 30-day mortality rate of about 11% in Denmark for colonic cancer remained stable in the period 1985-2004 according to data from the hospital discharge registries adjusted for age and gender (II). That of rectal cancer fell non-significantly from 5% to 4% (II) and remained at 4% in 2006 (110). From 2001, the 30-day mortality rates of colorectal cancer have been monitored in the clinical database of the DCCG. The overall 30-day mortality was 8.5% for patients registered in the DCCG database during the period 2001-2008 (17). Stratifying for urgency of surgery, the DCCG reports mortality rates of 6.2% after elective surgery and 22.1% after emergency surgery for the 2001-2008 period (17). The DCCG publishes annual rates only for those who have had emergency surgery and for the proportion who have had curative surgery in an elective setting. The temporal pattern of the latter has decreased slightly, as shown in **Table 5**.

**Table 5**

**30-day mortality (%) for Danish colorectal cancer patients after elective, curative surgery, 2001-2008, DCCG data (17,58)**

| Year of diagnosis | 2001 | 2005 | 2008 |
|---|---|---|---|
| Colon | 5.8 | 4.7 | 4.2 |
| Rectum | 4.4 | 3.3 | 2.9 |

A strong age - ASA – mortality dependency is present as illustrated in the annual DCCG reports showing increasing mortality along with increasing age and ASA score (17), Section 6.1.3.

An alarming discrepancy of the postoperative mortality rates exists between Denmark and its neighbouring countries, as illustrated in **Table 6**. The 30-day mortality in Denmark was about twice as high as in Norway, Sweden and Scotland, though data from the other countries are older than the Danish data.

**Table 6**

**Overall unadjusted 30-day mortality (%) after colorectal cancer surgery in Denmark and neigbouring countries**

| Country | Study characteristics | Time period | 30-day mortality (%) |
|---|---|---|---|
| Denmark (17) | National data, register-based n = 23,222 | 2001 – 2008 | Elective: 6.2% Emergency: 22.1% |
| Sweden (97) | Population-based n = 2,775 | 1996 – 2000 | Elective: 3.1% Emergency: 11.2% |
| Norway (98) | Population-based n = 1,129 | 1993 – 2007 | Elective: 3.5% Emergency: 10.0% |
| Scotland (111) | Population-based n = 3,200 | 1991 – 1994 | Elective: 2.8% Emergency: 8.2% |
| Northern Region of England (99) | Population-based n = 7,411 | 1998 – 2002 | Elective: 5.4% Emergency: 18.7% |
| Netherlands[1] (95) | Population-based n = 67,594 | 1994 – 1999 | Elective: 3.9% Emergency: 14.3% |

[1] Included resection surgery only, but not (sub)total colectomy. Outcome measure was in-hospital mortality.

Thus, the inferior short-term outcome in Denmark will contribute to the inferiority also of the long-term outcome compared with the outcomes reported for other countries – given that (i) the effectiveness of the oncologic treatment and (ii) the case-mix of the populations are comparable between the countries.
A different stage distribution between countries has been observed and debated (2,9), among others in lung cancer (112) and breast cancer (113). Supplementing data from the national cancer registries in the North with data from the national clinical databases like the DCCG, Folkesson documented that Danish rectal cancer patients were diagnosed at a later stage than other Nordic patients in 1997 (114). Such uneven stage distribution may contribute significantly to the higher mortality within the first half year - given that the preoperative evaluation for distant metastases and the histological examination for regional metastases were comparable between countries.
Nickelsen reported a 30-day mortality stratified for outcome of surgery, but not for urgency of surgery, for the period 2001-2002 based on DCCG data (115). Curative surgery was associated with a 30-day mortality of 7.2% for colonic cancer and 5.3% for rectal cancer, while the corresponding figures for palliative surgery were 20.7% and 14.7%, i.e., three times that following curative surgery. Except for emergency patients, Section 6.1.6, more up-to-date analyses of outcome are only available for curative outcome. The 30-day mortality after curative surgery in the entire 2001-2008 period was 6.4% for colonic cancer and 4.0% for rectal cancer (17), i.e., reduction in mortality was seen over time. A French population-based study of patients diagnosed during 1976-1995 reported the 30-day mortality by outcome of surgery.

The results were in line with those reported for the Danish setting and the 30-day mortality rate after palliative surgery was 15.6% in the period 1992-1995 (116). Patients who underwent palliative surgery were those who had incurable distant metastases and patients in whom local tumour control was impossible.

Thus, faced with the fact that 18% of Danish patients present with distant metastases and that curative surgery is not achieved in about 22% of Danish patients (17), the Danish short-term outcome is indisputably inferior to that achieved in other, comparable countries.
Postoperative death has always been an issue causing much concern and major efforts have been made to avoid such deaths. Several risk scoring systems have been designed to predict the risk of death. Specific for colorectal surgery is the ColoRectal - Physiological and Operative Severity Score (CR-POSSUM) (107) and the Association of ColoProctology score (ACP score) (108). Most risk scoring systems use a diverse range of preoperative variables, and some also deploy intra-operative and postoperative variables. A major criticism against the use of these risk scoring systems is that they are too complicated for use in daily practice and most have been developed for surgical audits only. None of them have been evaluated in Danish colorectal cancer patients.

### 6.1.2. Elderly patients
The Danish population is ageing and the number of elderly colorectal cancer patients is increasing.
The definition of elderly persons varies considerably in the international literature with cut-point for elderly ranging from ≥65 years (117,118) to ≥80 years (119,120). In present thesis, elderly persons are defined as persons aged >75 years if not otherwise reported.
Elderly persons bear a disproportionate burden of cancer and also a burden of other age-related health problems, including comorbidity (121). This unfortunate situation complicates decision-making in cancer treatment because of the elderly patient's increased vulnerability and thus reduced ability to withstand potential complications.
The term frailty is commonly used to describe an elderly person at heightened vulnerability to adverse health status change (122) because of his or her reduced reserve capacity. Frailty should be distinguished from aging and comorbidity, but all three are interrelated. In geriatric oncology, a comprehensive geriatric assessment is commonly performed to identify frailty in an elderly. Comprehensive geriatric assessment is a systemic approach aiming to assess physical functioning, comorbidity, polypharmacy, nutrition, cognition and emotional status. Patients are categorized into 'fit', 'intermediate' and 'frail' patients (123). Overall, 6-15% of elderly are considered to be frail (124). Data on elderly undergoing surgical cancer treatment document that frailty rather than age alone is related to postoperative morbidity (123,125). Data on frailty and mortality have not yet appeared.
Disparity in cancer treatment of elderly patients has been reported in several populations, including, among others, that the rate of patients undergoing surgery is lower among elderly than among their younger counterparts (96,126-136). Using data extracted from 15 European cancer registries, the EUROCARE study noticed that in 1987 the resection rate for colorectal cancer patients was 85% for patients aged <65 years, irrespective of their tumour site, but only 70-73% for patients aged >74 years with lowest rate for rectal cancer (126). The resection rate is stage-dependent with a lower resection rate among elderly suffering from palliative stage disease as compared with younger patients

(129,135,136). However, also the curative resection rate is lower among elderly than among younger patients (96,120,137). Furthermore, the rate of emergency surgery is higher among elderly with rates of 18% among patients aged 74-85 years and 29% among patients aged ≥85 years in contrast to 15% among patients aged 65-74 years (138). In the period 2001-2008, the emergency surgery rate among Danish patients aged >70 years was 17%, while that of their younger counterparts was 14% (17).

Thus, the short-term outcome in general, and the 30-day mortality for those elderly who receive surgical treatment in particular, is influenced by several factors making the interpretation of mortality difficult.

The curative resection rate among elderly patients aged >75 years has increased dramatically in Denmark from 36% in 1977-1982 to 49% in 1995-1999 according to data from the Danish Cancer Registry. The most prominent progress has been observed among patients aged 81-85 years and patients ≥86 years (III). In 1995-1999, patients aged 81-85 years underwent curative resection almost as frequently as patients ≤75 years, i.e., about 50%. Similarly, the proportion of elderly who received 'no' or 'symptomatic treatment only' fell from 20% to 13%, while this proportion declined from 14% to 10% among their younger counterparts. A declining divergence in the curative resection rate between patients <75 years and elderly was also observed in France during the period 1976-1999 and it was mainly ascribed to a rise in the resection rate among elderly over time (137,139). In France, the curative resection rate among elderly patients was 72% in colorectal cancer combined during 1988-1999 (137). In contrast, the resection rate in elderly patients aged 80+ years with curative-stage colonic and rectal cancer in the Southern Netherlands has been at least 96% and 88%, respectively, since 1985 (134).

The age-dependent decrease of 30-day and 6-month relative survival in Denmark in 1995-1999 is shown in **Table 7**, (III). Previously, in 1977-1982, this age-depency was even greater, but 30-day and 6-month relative survival have improved markedly, by 6-17%, among the elderly over time and by 2-6% among their younger counterparts - even though more elderly underwent surgery.

A notable decrease in relative survival was observed between 30 and 180 days after surgery, particularly among the elderly, which is in line with observations made in the Netherlands (140) and the England (141). The Dutch study, in which very fit elderly had preoperative short-course radiotherapy in addition to TME surgery, reported that the excess mortality within 6 months of surgery was caused by non-cancer mortality and that postoperative complications more often had a fatal course among elderly than among younger patients (140). For instance, anastomotic leakage occurred at a similar rate in elderly and younger patients, but the 6-month mortality was 57% in the elderly compared with 8% in the younger patients (142). A similar tendency was observed for other surgical complications and several medical complications (142). Others have confirmed that postoperative mortality

especially among the elderly extends beyond the 30 days after surgery and that the 30-day mortality rate understates the true risk of dying after surgery (141,143). Typically, patients dying between 30 and 90 days postoperatively were elderly, high-risk patients developing complications who had a prolonged course of intensive care, which ultimately culminated in multiorgan failure and death (143).

Based on DCCG data from 2001-2008, the 30-day mortality of 15.0% in patients aged >70 years remains much higher than that in the younger patients aged ≤70 years (3.6%) (17) - despite continuing advances in peri-operative care, a progress assumed to be important, in particular in frail, elderly patients. In line with the Danish figures, a mortality rate among elderly patients exceeding that of their younger counterparts at least two to three times higher has repeatedly been reported in other populations (95,96,116,127,128,130,131,135,136,144,145). In the UK, for example, the 30-day mortality rate was 10.6% in elderly >75 years and 3.8% in their younger counterparts in the period 2000-2005 during which 85% of the elderly underwent surgery (131). Few series on selected patients report comparable mortality rates between elderly and younger patients (146).

Thus, it must be expected that the observed improved short-term survival and increasing resection rate among the elderly contributes to improve their long-term survival as well.

### 6.1.3. The impact of comorbidity

Because of their age, colorectal cancer patients are likely to suffer from comorbid diseases. The proportion of Danish colonic cancer patients with comorbidity documented in hospital discharge registries and determined by Charlson's Comorbidity Index scores 1-2 and 3+ increased from 30% in 1995-1997 to 43% in 2004-2006 and for rectal cancer patients from 30% to 37%, i.e., at least one-third of the patients had comorbidities (VI). About 10% of the patients scored 3 or more, i.e., had severe comorbidity, regardless of tumour origin. The increase in comorbidity score may partly be due to a more accurate coding practice in the hospital discharge registries as a consequence of a change in administrative reimbursement.

Comorbidity affects the surgical decision-making for Danish colorectal cancer patients as evidenced by a decreasing resection rate by increasing comorbidity level (VI), **Table 8**.

**Table 8**

**Resection rates (%) of 3,433 Danish colorectal cancer patients by comorbidity level, 2004-2006**

| Charlson Comorbidity score | 0 | 1-2 | 3+ |
|---|---|---|---|
| Colonic cancer | 82.7 | 78.2 | 67.6 |
| Rectal cancer | 70.6 | 61.0 | 51.6 |

**Table 7**
**Relative survival of 69,562 Danish colorectal cancer patients by age, 1995-1999 (% (95% CI))**

| Age group | ≤ 60 | 61-75 | 76-80 | 81-85 | 86+ |
|---|---|---|---|---|---|
| Relative 30-day survival | 97 (97-98) | 94 (93-94) | 91 (90-92) | 86 (85-88) | 82 (80-84) |
| Relative 6-month survival | 87 (86-88) | 81 (80-82) | 75 (73-77) | 70 (68-72) | 62 (59-64) |

Among those about 10% of the colorectal cancer patients who suffered from severe comorbidity, only about one-half to two-thirds underwent the mainstay of treatment: surgical resection. The resection rates among colonic cancer patients with Charlson Comorbidity scores 1-2 and 3+ were even lower in 1995-1997, while no change over time was observed for rectal cancer patients.

The treatment policy for patients with colonic and rectal cancer and concomitant severe comorbidity in Denmark has seemingly changed differently over time. In the period 1995-2006, 'no surgical intervention' was performed in almost one-third of colorectal cancer patients with severe comorbidity; yet, the rate of 'no surgical intervention' was twice or trice as high as among patients with a Charlson Comorbidity score of zero (VI). However, the rate of 'no surgical intervention' has decreased over time in colonic cancer patients with severe comorbidity to 30% in 2004-2006. In contrast, in rectal cancer the rate rose to 37% in 2004-2006. In addition, about 5% of all colonic cancer patients and 10-15% of all rectal cancer patients had a diversion or a local procedure, including SEMS insertion, with slight declines over time among patients with severe comorbidity.

Thus, colonic cancer patients increasingly underwent resection, while they less frequently underwent a diversion/local procedure or had 'no surgical treatment'. In rectal cancer, however, the resection rate remained stable, but the patients less frequently had a diversion/local procedure and 'no surgical treatment' became increasingly common. In other words, over time the treatment of patients with severe comorbidity has become surgically more aggressive in colonic cancer, while apparently becoming more cautious or differentiated in rectal cancer. This change is hardly caused by an increase in the proportion of later-stage disease among patients with severe comorbidity as stage distribution remained stable in Denmark during that time period. The finding of an inverse relationship between the comorbidity level and the resection rate in Danish colorectal cancer contradicts observations of other studies (147-149), but these studies did not differentiate between the outcomes of surgery and confounding by cancer treatment may therefore bias their results. The resection rates in the Dutch studies were much higher (above 87% in colonic cancer and above 67% in rectal cancer) and they were independent of comorbidity levels (148); and for patients with stage I-III, the resection rates were above 95% regardless of comorbidity (149). Noticeably, as compared with other European populations, a much higher proportion of Danish patients with severe comorbidity are either not offered optimal cancer treatment, i.e., surgical resection, or they refuse surgery themselves. Clinicians may be concerned whether comorbid patients succumb during the postoperative course, whether they can sustain the toxicity of chemotherapy/radiotherapy or whether they would have any survival benefit at all taking their remaining life expectancy into consideration. In contrast to the resection rate, non-Danish studies have reported that comorbidity can limit the choice between treatment regimens as documented by the less frequent use of adjuvant chemotherapy in patients with stage III colon cancer (148,150) and the less frequent use of adjuvant radiotherapy in patients with rectal cancer (148). When considering the impact of comorbidity on outcome, it should also be remembered that measurement of comorbidity does not necessarily parallel for example 'general functional status' or 'performance status', which may be the factor that determine clinicians' daily decision-making. Finally, the skewed resection rates among co-

morbid patients across countries may find a methodological explanation in an unequal registration of such patients. Thirty-day mortality rates according to the Charlson Comorbidity level are unavailable for Danish colorectal cancer patients. The overall 30-day mortality rate in Denmark after resectional surgery remained stable at about 8% in colonic cancer and at about 6% in rectal cancer from 1995-1997 to 2004-2006 even if a growing proportion of colonic cancer patients with comorbidity underwent resection (VI). During the same period, the 30-day mortality rates for those 5% of the colonic cancer patients who had a diversion/local procedure ranged from 27% to 36% with no temporal pattern. For the 10-15% of rectal cancer patients who had such a palliative procedure, the mortality rates remained at the level of 11-14%.

Thus, the postoperative mortality rates remained stable in spite of an altered surgical treatment regimen for patients with severe comorbidity.

The ASA score may be expressed as a score describing the severity of comorbidity. Based on the DCCG data from 2001-2008, the 30-day rate of mortality from colorectal cancer rises dramatically by increasing ASA score (17), **Table 9**. Almost every fourth patient had severe comorbidity as determined by an ASA of III or more.

**Table 9**

**Relationship beween ASA score and 30-day mortality (%) for Danish colorectal cancer patients based on DCCG data, 2001-2008**

| ASA | I | II | III | IV | V | Missing |
|---|---|---|---|---|---|---|
| Proportion of patients (%) | 19 | 44 | 21 | 3 | <1 | 13 |
| 30-day mortality | 1.8 | 5.6 | 17.7 | 37.3 | 69.0 | NA |

These data clearly illustrate that comorbidity has a profound impact on the short-term survival of colorectal cancer patients. A similar relationship has been observed among English colorectal cancer patients (151) and among Swedish rectal cancer patients, although the mortality rates were at least two-fold lower in the Swedish population (152). In England, the overall 30-day postoperative mortality rate was 6.7% in 1998-2006, but 24.2% in patients with a Charlson Comorbidity score 3+ (E Morris, personal communication). Other population-based studies support that short-term survival is negatively influenced by comorbidity (147,149). A recent study based on DCCG data showed that the observed association between socioeconomic status (SES) and 30-day mortality of elective patients was mediated mainly through differences in comorbidity level and to some extent lifestyle, such as tobacco and alcohol consumption (153). In other words, patients with a low SES had a higher 30-day mortality which mainly was attributable to a higher comorbidity level.

### 6.1.4. Seasonal variation
Peaking during the winter months, mortality rates for cardiovascular and respiratory diseases (154-158) as well as influenza and other respiratory tract infections (159) exhibit distinct seasonal variation. The most plausible explanation is a well-recognised inverse association between outdoor temperature and morbidity and mortality, but also that elderly may be even more prone to

the effects of cooling because they are less able to regulate body temperature (160).

Based on the facts, first, that comorbidity has much impact on short-term and long-term survival from colorectal cancer (VI), and, second, that postoperative medical complications, e.g., heart failure, sepsis and respiratory insufficiency, have been shown to be the main cause of early death after emergency surgery for colonic cancer (VIII), it seems likely from a theoretical point of view that 30-day mortality after surgery for colorectal cancer exerts some seasonal variation as well with highest rates seen in the winter months. However, a nationwide study including 33,556 patients who underwent surgery for colorectal cancer failed to document such a winter peak of the monthly 30-day mortality rates (VII).

Instead, and unexpectedly, the study observed a non-significant increase in the 30-day mortality rate in July with a rate of 10.0% (95% CI: 8.9-11.0%) as compared with the overall 30-day mortality rate of 8.7% (95% CI: 8.4-9.0%), **Figure 4**. The peak-to-trough ratio was 1.05 (95% CI:1.00-1.16), but this figure should be interpreted with caution because the monthly variation demonstrated no single annual cycle.
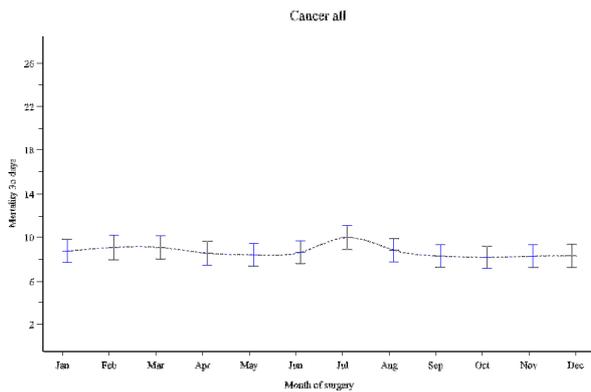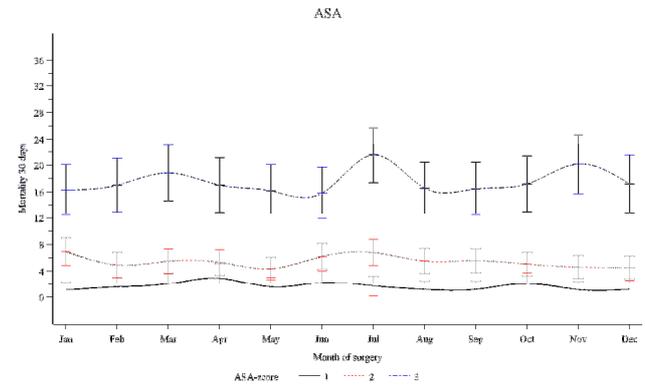


**Figure 4**
**Monthly 30-day mortality rates for 33,556 patients after surgery for colorectal cancer, 1996-2006.**

The overall 30-day mortality rate of colonic cancer was 9.8% (95% CI: 9.4-10.2%) and of rectal cancer 6.5% (95% CI: 6.1-7.0%). The monthly 30-day mortality rates after surgery for colon cancer exhibited an even greater seasonal variation than the entire group with a non-significant 18% increase in July which should be seen in light of the 30-day mortality rate of 11.6% (95% CI: 10.2-13.1%). For rectal cancer, the monthly mortality rates were almost stable throughout the calendar year, although a minor 15% increase was seen in February with a 30-day mortality of 7.5% (95% CI: 5.8-9.2%).

Although the Danish study (VII) found no significant seasonal variation in 30-day mortality after surgery for colorectal cancer although 78% of the colorectal patients suffered from comorbidity based on the ASA score, the Paper does not, however, preclude a negative effect of coexisting comorbidities on the short-term survival after colorectal cancer surgery. It is noteworthy that an ASA score ≥III was associated with a pronounced, but statistically non-significant seasonal variation in the 30-day mortality rates with a peak in July, **Figure 5**. In July, the 30-day mortality was 21.5% (95% CI: 17.4-26.0%), a 24% increase. No seasonal

variation was depicted in monthly 30-day mortality rates for patients with ASA scores I and II, **Figure 5**.



**Figure 5**
**Monthly 30-day mortality rates for 14,073 patients after surgery for colorectal cancer stratified by the ASA score, 2002 through 2006.**

To our knowledge, the literature contains no other studies examining seasonal variation in postoperative mortality from colorectal cancer. The July effect was unexpected and the most obvious explanation, although it is speculation only, is that July is the summer holiday month in Denmark, and thus staffing levels are low at all hospitals, i.e., standby is reduced. All elective activities, except cancer treatment, in hospitals are reduced during summer vacation. Therefore, there are fewer surgeons available to do surgery and fewer experienced surgeons to supervise more challenging operations, fewer anaesthesiologists to conduct the anaesthesia in high-risk patients with comorbidities, and fewer nurses to observe the patients in the wards postoperatively, all of which may contribute to inferior management of the patients. A July effect was not seen for rectal cancer, probably because the management of rectal cancer since the late 1990s has been centralized and the majority of patients are being treated by consultant surgeons only at high volume hospitals who may have a better standby during summer vacation. Thus, rectal cancer patients seem to be spared the deleterious effect of vacation and low staffing levels. A very recent Swedish small-scale study reported that the frequency of colonic cancer patients presenting as emergency cases doubled in the summer months (161), which partly could explain the July effect. However, the proportion of the Danish emergency cases remained stable throughout the calendar year.

A very recent large-scale population-based study from London and the South East of England analysed seasonality in mortality within the first month of diagnosis (not identical to 30-day postoperative mortality rate) in colorectal cancer patients (162). Diagnosis in the summer was associated with a decreased mortality compared with winter, which is completely opposite of the Danish study. However, seasonality in mortality disappeared when adjusting for monthly variations in general population mortality.

Thus, to date, there is no hard evidence of any seasonality in short-term mortality from colorectal cancer, although the July effect should be elucidated further.

| Postoperative mortality (No. of studies) | Hospital caseload | Surgeon's caseload | Surgeon's education | Surgeon's experience | Type of hospital |
|---|---|---|---|---|---|
| Colonic cancer, n = 12 | Strong | Strong | Strong [II] | Strong [I] | NA |
| Rectal cancer, n = 8 | No | No | No [II] | No [I] | No [II] |
| Colorectal cancer[III], n = 14 | No | No | Weak | NA | No |

[I] Based on one study, [II] Based on two studies, [III] Based on studies not stratified for tumour origin, NA: not applicable

**Table 10**

**Strength of evidence for an association between selected variables and postoperative mortality**

### 6.1.5. Caseload and surgical specialty

The benefit of centralization and specialization has been debated ever since Luft in 1977 suggested that certain operations should be regionalised because outcome of complex procedures improved the more operations were performed (163). Afterwards, the volume-specialty-outcome relationship has been repeatedly demonstrated for surgically complex procedures that involve a high risk of postoperative mortality, such as pancreatic cancer surgery (164,165) and oesophageal cancer surgery (165).

In a review of the literature from 1992 through June 2004 on studies including at least 500 patients reporting short-term out-

come following surgery for colorectal cancer, n = 35, the interpretation of the association between the volume-specialty variables and the postoperative mortality following surgery for colonic cancer, rectal cancer and colorectal cancer was as listed in **Table 10** (IV).

The association between hospital caseload and postoperative mortality was most frequently analysed, **Figure 6**. Postoperative mortality after colonic cancer surgery was significantly associated with hospital caseload, OR 0.64 (95% CI 0.55 to 0.73), **Figure 6**, and the surgeon's caseload, OR 0.50 (95% CI 0.39 to 0.64). Few, heterogeneous studies have examined the influence of the surgeon's education/specialty and experience on the postoperative mortality from colonic cancer. They found an improved outcome among patients who were managed by board-certified surgeons/colorectal surgeons compared with non-board certified surgeons/colorectal surgeons or experienced surgeons (>20 yrs. vs. <5 yrs.). Only few, mainly small-scale studies, mostly flawed by methodological heterogeneity, have been performed on rectal cancer to examine these relationships.
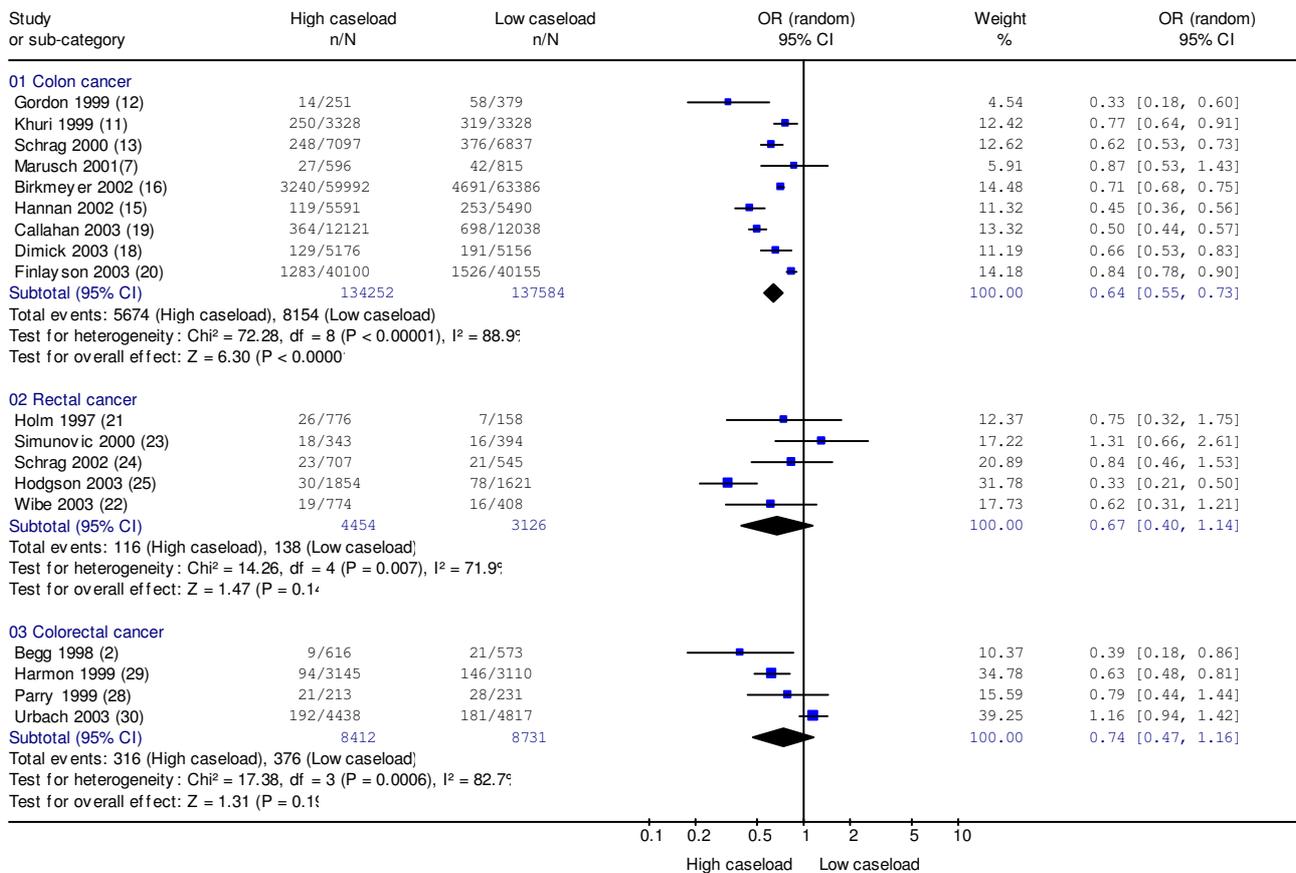


**Figure 6**
**Hospital caseload and postoperative mortality in colorectal cancer surgery. Forest plot of reviewed studies stratified for tumour origin (colonic, rectal, colorectal). Citations numbered as in (IV).**

Thus, the review furnished evidence of an association between a lower postoperative mortality from colonic cancer and high hospital caseload, high surgeon's caseload, board-certification and/or surgeon sub-specialty and long experience of the surgeon. Such an association could not be identified for rectal cancer; however, many of the rectal cancer studies were flawed by methodological heterogeneity. Importantly, no studies reported an inverse association.

Compelling evidence of the volume-outcome relationship has emerged since Iversen's review (IV) was published. More recent reviews including the most recent studies report findings supporting the positive associations listed in **Table 10** (166-169); the reviews of Salz (166) and Archampong (169) analysed rectal cancer only. Nugent concluded that mortality from rectal cancer was not associated with hospital volume, but with surgeon volume (170).

The observed relationship between hospital and surgeon volume and postoperative mortality in recent population-based studies (in which adjustment for case-mix was made) is shown in **Table 11**. In rectal cancer, recent studies seem to confirm a volume-outcome association.

A Danish nationwide study has examined the volume-outcome relationship among colonic cancer patients undergoing emergency surgery. It failed to identify such a relationship with cut-points for caseload of ≤12 vs. ≥21 operations yearly (VIII). Two-thirds of the patients underwent surgery at hospitals treating ≤20 emergency patients yearly. In other words, the majority of the patients were treated at low-volume hospitals and the analysis comprised almost exclusively low-volume hospitals. A large-scale English population-based study on emergency colorectal surgery in which about one-third of the patients suffered from colorectal cancer also failed to identify a volume-outcome relationship in adjusted analyses (178).

The specialty-outcome association has been scarcely analyzed, but such an analysis may be difficult to perform because there is no internationally agreed definition of a specialist.

Considering the greater complexity of rectal cancer surgery than of colonic cancer surgery, it seems striking that hospital and surgeon caseload predicted postoperative mortality for colonic cancer only in the meta-analysis, **Figure 6**. The reason may be that about 14% of colonic cancer patients require emergency surgery, which can be technically (very) challenging and is associated with much increased postoperative morbidity and mortality ratios. Such patients may undoubtedly benefit from assistance from specialized anaesthesiologist and cardiologists, ICU, etc., i.e., services most frequently available at hospitals with a high caseload in which surgeons having a high caseload are more likely to work. Interestingly, in 2007 a US SEER study on postoperative mortality in colonic cancer observed a hospital volume-outcome association that was mainly attributable to the availability of clinical services such as cardiac care units, around-the-clock availability of intensive care units, multiple medical specialties and interventional radiology, among others. Such resources may facilitate timely management of any complication (174). As in most US studies, hospital and surgeon volumes were very low.

Thus, the finding of the volume-outcome relationship in colonic cancer seems reasonable and volume may be a surrogate marker or proxy for other important structural factors such as quality and capacity of the ICU, availability and capacity from other specialties, multidisciplinary infrastructure and nurse staffing, among others.

**Table 11**

**Postoperative mortality: Volume-outcome association in recent population-based studies**

| Postoperative mortality | Colonic cancer | | Rectal cancer | |
|---|---|---|---|---|
| | Hospital caseload | Surgeon's caseload | Hospital caseload | Surgeon's caseload |
| Harling 2005 (10) | | | - | NA |
| Engel[1] 2005 (95) | - | NA | - | NA |
| Ho 2006 (171) | + | + | + | + |
| Rogers 2006 (172) | + | + | + | - |
| Simunovic 2006 (173) | - | NA | | |
| Billingsley 2007 (174) | + | + | | |
| Morris[II] 2007 (175) | NA | - | | |
| Billimoria 2008 (176) | + | NA | + | NA |
| Kressner 2009 (177) | | | + | NA |
| Elferink 2010 (135) | - | NA | | |
| Elferink 2010 (136) | | | + | NA |
| Borowski 2010 (99) | - | + | - | - |

- indicates lack of a positive association (not a negative association).
[I] Included resectional surgery only, but not (sub)total colectomy.
[II] Included curatively treated stage II colonic cancer only.

The results of volume-specialty-outcome studies are difficult to interpret because methodological issues may be many and because they do not lend themselves easily to clear-cut black-or-white conclusions. Case-mix differences among hospitals and surgeons may bias the volume-specialty-outcome relationship. Even if adjustment for case-mix is performed, a skewed case-mix may persist. We may, for instance, ask ourselves whether treatment policy for elderly and comorbid patients are similar among different hospitals or if some hospitals abstain from offering frail patients surgery. Such confounding by indication would favour hospitals treating the less frail patients. The question may also be asked whether all hospitals are evenly aggressive in performing radical surgery, which may heighten the risk of complications, or if some hospitals perform less aggressive, low-risk surgery with better short-term outcome at the expense of a higher rate of non-radical surgery. These important confounding factors have not been adjusted for why results of volume-specialty-outcome studies should be interpreted very cautiously.

Clustering is the phenomenon that patients' characteristics are likely to be similar for the same hospitals or surgeons and to differ between hospitals or surgeons (179). If clustering is not adjusted for, any observed difference in outcome may falsely favour volume. For instances, the characteristics of the inhabitants within one catchment area may differ from those of other catchment

areas. For example, a skewed proportion of inhabitants in terms of adverse life-style will affect comorbidity; similarly, young, fit patients with high SES may prefer treatment at university or high-volume hospitals and not at local or low-volume hospitals, and so on.

There is considerable variation in the definition of high and low caseload across the studies reviewed above. No studies have yet been able to define minimal caseload standards for achieving better outcome. For colonic cancer, cut-points for low hospital caseload ranged between 10 and 61 and for high hospital caseload between 19 and 201 (IV). For rectal cancer, the respective figures were 5 to 20 and 10 to 40. The definitions used to describe the surgeon's caseload differed more for colonic cancer than for rectal cancer. The results obviously depend on these definitions and as suggested by Chowdhury, the volume-outcome relation would be more accurately captured if resort was made to graded volumes (for instance: 0-20, 21-40, 41-60, and so on) rather than arbitrarily defined volumes (180). Further, many studies are too poorly powered to detect a difference in outcome, which may flaw the rectal cancer studies most because the postoperative mortality from rectal cancer is lower than that from colonic cancer.

The volume-specialty-outcome relationship remains a matter of much controversy. In 2004, a task group nominated by the National Board on Health recommended that the surgical management of colorectal cancer should be practised at no more than 10-15 units in Denmark (181). However, in 2010 colonic cancer surgery was still being performed at 20 departments and rectal cancer at 17 departments, Section 3.4. In 2008, the annual hospital caseload for colonic cancer in Denmark ranged from 32 to 209, excluding three outliers treating 13, 16, and 16 patients, respectively. The caseload for rectal cancer ranged from 43 to 155, excluding eight outliers treating 2, 2, 3, 5, 5, 7, 8, and 9 patients, respectively (17). Some departments treated only one or two colorectal cancer patients weekly.

The benefit of high volume and specialization on postoperative mortality seems evident in colonic cancer and probably also in rectal cancer. Moreover, the fact that no studies have so far reported detrimental effects of high caseload or specialization must be emphasized. A large-scale US study has recently reported that colonic cancer patients who underwent surgery at a hospital with an annual caseload of less than 42 patients had a 23% higher risk of death than those who underwent surgery at a hospital treating more than 125 patients per year (176). Similarly for rectal cancer, patients treated at hospitals with less than 10 patients per year had a 33% higher risk of death than patients who underwent surgery at hospitals treating more than 34 patients per year. However, volume-outcome relationship or not, there are other compelling reasons for favouring centralization. For instance, high-volume surgeons may be better equipped to prevent, recognize and manage postoperative complications.

### 6.1.6. Emergency surgery for colonic cancer

The postoperative mortality rate following emergency surgery for colorectal cancer in Denmark is high (22%) as reported in Section 6.1.1., (VIII) (17). The rate of rectal cancer patients undergoing emergency surgery is extremely low, so emergency surgery is performed almost exclusively in colonic cancer. Patients presenting as emergencies have a more unfavourable prognosis than elective patients for a number of reasons: they are older and have later-stage disease, among others, (182,183).

In the Danish population of 2,157 emergency patients from 2001-2005, surgery was performed mainly because of bowel obstruc-

tion (73.9%) and perforation (21.3%) (VIII). The median time from the first contact to hospital to emergency surgery was 1 day (inter-quartile range: 0-3). The 30-day mortality decreased non-significantly from 23.2% in 2001 to 19.8% in 2005.

The 30-day mortality was significantly associated with the postoperative course, **Table 12**.

**Table 12**

**30-day mortality by the number of postoperative complications**

| No. of postoperative complications (proportion of patients) | n = 0 (59.3%) | n = 1 (27.8%) | n = 2 (8.1%) |
|---|---|---|---|
| 30-day mortality (%) | 8.5 | 39.4 | 47.4 |

Surgical complications occurred among 20.5% of the patients and had no statistically significant influence on their 30-day mortality, 20.8%, **Table 13**. In contrast, 24.4% of the patients developed medical complications (cardiopulmonary, renal, thromboembolic and infectious) and their mortality was 57.8%. Included in these complication rates were 5.1% of the patients who developed surgical and medical complications combined; their 30-day mortality was 34.2%. Excluding pneumonia, other infectious diseases and deep venous thrombosis, the 30-day mortality increased to at least 50% in case of a medical complication.

Independent risk factors for death within 30 days after surgery were all of age ≥71 years, male gender, ASA grade ≥ III, palliative outcome, free or iatrogenic tumour perforation, splenectomy, intraoperative surgical adverse events and postoperative medical complications, **Table 14**. Hartmann's procedure was associated with a more favourable outcome than other conditions.

Thus, the main contributors to postoperative mortality after emergency surgery for colonic cancer were those almost 30% of the patients who were aged >80 years and who therefore had an at least five-times higher risk of death than other patients, and those 24% of the patients who developed medical complications and who therefore had a 12-times higher risk of death. Additionally, about one third of the patients had ASA ≥ III and a two-three-times higher risk of death. Prevention and/or early recognition of medical complications combined with appropriate treatment is expected to substantially reduce the 30-day mortality after emergency.

Age, comorbidity and social deprivation were all identified as strong independent risk factors of death after emergency colorectal surgery in an English population-based study in which almost 20% of the patients had cancer (184). The study analysed only patient-related preoperative variables and thus not postoperative complications.

Postoperative medical complications counting pneumonia as the most frequent were also very frequently reported in a US study of 292 elderly patients undergoing emergency colorectal surgery among whom 30% had obstructed or perforated colonic cancer (185). The development of postoperative complications was the strongest risk factor for death, OR 36 (95% CI 11-114). The authors emphasized the inappropriate coincidence of the reduced physiological reserves in the elderly, their higher frequency of concomitant comorbidity and the time constraints associated with emergency surgery which precludes detailed medical workup and intervention.

**Table 13**

Postoperative data for 2,157 Danish patients undergoing emergency surgery for colonic cancer, May 2001 - December 2005 and univariate analysis of factors associated with postoperative mortality (VIII).

| Variable | No. of patients (%) | No. of deaths within 30 days after surgery (%) | P |
|---|---|---|---|
| Surgical complications | | | 0.283 |
| Total[1] | 441 (20.5) | 89 (20.8) | |
| Afterbleeds requiring surgery | 19 (0.9) | 7 (36.8) | |
| Wound dehiscence[2] | 106 (4.9) | 18 (17.0) | |
| Anastomotic leak requiring surgery[3] | 73 (6.3) | 18 (24.7) | |
| Anastomotic leak, conservative treatment[3] | 12 (1.0) | 5 (41.7) | |
| Intestinal obstruction requiring surgery[2] | 26 (1.3) | 8 (30.8) | |
| Stoma complications requiring surgery[4] | 42 (5.1) | 7 (20.0) | |
| Wound abscess[2] | 146 (7.1) | 17 (11.6) | |
| Medical complications | | | <0.0001 |
| Total[1] | 526 (24.4) | 304 (57.8) | |
| Apoplexy | 28 (1.3) | 14 (50.0) | |
| Myocardial infarction or heart failure | 180 (8.4) | 128 (71.1) | |
| Pneumonia | 159 (7.4) | 52 (32.7) | |
| Aspiration | 31 (1.4) | 20 (64.5) | |
| Artificial respiration | 132 (6.1) | 75 (56.8) | |
| Sepsis | 160 (7.4) | 108 (67.5) | |
| Need for dialysis | 44 (2.0) | 30 (68.2) | |
| Pulmonary embolism | 17 (0.8) | 11 (64.7) | |
| Other complications | | | <0.0001 |
| Unspecified | 21 (1.0) | 12 (57.1) | |

Only postoperative complications occurring in (a) at least 5% of patients or (b) at least 1% of patients combined with a 30-day mortality rate >25% are shown.
[1]Including 111 patients who had surgical as well as medical complications.
[2]Among 2,066 patients having a laparotomy. [3] Among 1,167 patients having right or extended right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoid colectomy or colectomy with an ileorectal anastomosis. [4] Among 822 patients having a stoma, i.e., Hartmann's procedure, colectomy + stoma, palliative stoma or a defunctioning loop-stoma.

Mortality increased significantly by the number of complications (VIII). A population-based US study on surgery for different conditions including colonic resections described how various medical complications multiply the risk of postoperative death (186). The authors also reported that even a mild first complication like pneumonia may multiply the risk of death by a factor of five and that the risk was equal for healthy patients and frail, high-risk patients, although the latter were at increased risk of developing a complication. These findings underscore the importance of preventing even mild complications.

**Table 14**

Multivariate analysis of factors associated with 30-day mortality after emergency surgery for colonic cancer in Denmark, May 2001 - December 2005 (VIII).

| Variable | Odds ratio (95% c.i.) | P |
|---|---|---|
| Age (years) | | <0.0001 |
| ≤50 | 1 | |
| 51-60 | 0.7 (0.2-2.1) | |
| 61-70 | 1.3 (0.5-3.4) | |
| 71-80 | 2.9 (1.2-7.4) | |
| 81-90 | 4.7 (1.9-12.1) | |
| ≥91 | 10.3 (3.6-29.5) | |
| Gender | | 0.048 |
| Male | 1 | |
| Female | 0.8 (0.6-1.0) | |
| ASA Grade | | <0.0001 |
| I+II | 1 | |
| III | 1.9 (1.4-2.5) | |
| ≥IV | 2.9 (2.0-4.3) | |
| Outcome of surgery | | <0.0001 |
| Curative | 1 | |
| Palliative | 2.3 (1.7-3.2) | |
| Not determinable | 1.1 (0.5-2.1) | |
| Missing[1] | 7.6 (1.4-41.8) | |
| Surgical procedure | | 0.024 |
| Right hemicolectomy[2] | 1 | |
| Left hemicolectomy | 0.9 (0.5-1.7) | |
| Sigmoid colectomy | 1.6 (0.9-2.8) | |
| Hartmann's procedure | 0.6 (0.4-0.9) | |
| Colectomy + IRA[3] | 1.1 (0.5-2.3) | |
| Colectomy + ileostomy | 1.2 (0.7-2.0) | |
| Palliative surgery[4] | 1.7 (1.0-2.9) | |
| Other | 1.3 (0.8-2.1) | |
| Tumour perforation | | 0.0004 |
| No or encapsulated | 1 | |
| Free | 2.1 (1.4-3.0) | |
| Iatrogenic | 2.4 (1.0-5.9) | |
| Resection of organs | | 0.039 |
| None | 1 | |
| Spleen | 2.4 (1.0-5.4) | |
| Intraoperative adverse events | | 0.011 |
| None | 1 | |
| Surgical[5] | 2.3 (1.2-4.4) | |
| Postoperative complications | | <0.0001 |
| None | 1 | |
| Medical | 11.7 (8.8-15.5) | |

[1] n = 27 [2] Right and extended right hemicolectomy and transverse colectomy. [3] IRA: ileorectal anastomosis. [4] Palliative stenting, palliative stoma, laparotomy only and local treatment. [5]Injury to the spleen, lesion of small bowel/colon and other surgical adverse events.

An unexpected finding in the Danish study (VIII) was that resection of neighbouring organs other than the spleen was not associated with an increased mortality risk. Resection of the spleen may reflect the performance of the surgeon rather than the complexity of the disease. More than one third of the patients underwent palliative surgery which doubled their risk of death within 30 days.

Thus, to increase the curative resection rate in emergency surgery and thus lower the postoperative mortality rate, surgeons should attempt to perform en bloc resection of locally advanced tumours adherent or fixed to for instance the abdominal wall, uterus, small bowel, etc.

### 6.1.7. Self-expanding metallic stents for acute bowel obstruction

About 14% of Danish colorectal patients present as surgical emergencies mainly because of acute bowel obstruction (VIII). Conventional therapy for relieving malignant bowel obstruction includes emergency surgery, e.g., resection, stoma formation, etc. Emergency surgery is associated with inferior short-term outcome, Section 6.1.6. An alternative approach for relief of bowel obstruction is SEMS insertion. After its first description in 1991 by Dohmoto (54), numerous publications have reported high technical and short-term clinical success rates of SEMS placement as summarized in recent reviews (187-189). Using meta-analytical techniques to analyse studies comparing outcome between SEMS placement and surgery for acute colorectal cancer obstruction (n = 8), data favoured the stented patients in terms of fewer post-procedural medical complications and lower post-procedural mortality (190). However, the review is flawed by lack of matching in the studies analyzed.

When SEMS placement is performed on the indication acute bowel obstruction, some patients, i.e. those with potentially curable disease, may afterwards undergo elective resection as bridge to surgery. In those patients who appeared to be incurable after diagnostic work-up, the SEMS may serve as a definitive palliative procedure. Awareness of the SEMS modality has recently been spurred by reports on stent-related bowel perforation (191,192). A Dutch randomized trial comparing stenting with surgery for incurable left-sided malignant bowel obstruction was even stopped prematurely because of an unacceptably high perforation rate in the stented group (193). Stent-related perforation may occur early during the SEMS procedure or within few days or perforations may be late, i.e., occurring ≥30 days after SEMS placement. Besides predilatation of the bowel obstruction, the reason for these perforations remains unknown. Yet, concern has centred on specific types of stents and concomitant chemotherapy (191,194,195).

To date, three Danish single-centre studies have been carried out on the short-term outcome of SEMS for acute malignant colorectal obstruction (196,197) (IX), **Table 15**.

One study included only the subgroup of patients with potentially curable colorectal cancer (IX). All studies were based on retrospective reviews of medical records, but patients were registered consecutively in one study (196). The outcome data are not fully comparable, among others because of the use of different definitions of clinical success, unknown follow-up time for perforation, etc. The technical and clinical success rates were quite similar to those reported in recent reviews (187-189). The difference in the proportions of patients who had SEMS as bridge to surgery reflects the heterogeneity of patients only.

The 12% perforation rate in the study of Iversen was rather high (IX). One of the four perforations was a blow-out in the caecum, while three were tumour perforations occurring 0, 5, and 17 days, respectively, after SEMS insertion. Emergency surgery was needed among 15% of the patients, including all four patients with perforation and one patient with insufficient relief of obstructive symptoms even after a second SEMS attempt. Three of the five patients who needed acute surgery developed medical complications (sepsis, prolonged fever and prolonged recovery because of poor general condition), while three of the 29 patients

who underwent elective resection developed minor postoperative complications (wound infection and urinary tract infection). Defined as mortality within 30 days after the SEMS attempt and surgery, the cumulative 30-day mortality was 3%; only the patient with blow-out perforation passed away. Pommergaard reported one fatal event after a perforation with a similar mortality rate although the follow-up time was not reported (197). In contrast, Bertelsen reported a cumulative 30-day mortality rate after SEMS and resection of 17% (196). However, the study included patients from the early beginning after SEMS implementation at the department reflecting that the surgeons were in the first phase of their learning curves (196).

**Table 15**

**Short-term outcome after SEMS in acute malignant colorectal obstruction based on Danish studies and a recent review**

| | Bertelsen (196) n = 56 | Pommergaard (197) n = 38 | Iversen[I] (IX) n = 34 | Review of Watt (189) median (range) |
|---|---|---|---|---|
| Study period | 1997-2004 | 2002-2007 | 2004-2007 | |
| Technical success | 88% | 97% | 100% | 96 (67-100)% |
| Clinical success | 75% | 97%[II] | 88% | 92 (46-100)% |
| Perforation | 2%[III] | 5% | 12% | 5 (0-83)% |
| 30-day mortality after SEMS | NA | 3% | 0% | NA |
| Elective bridge to surgery | 52% | 24% | 85% | NA |
| Cumulative 30-day mortality after SEMS and surgery | 17% | ? | 3% | NA |

[I] Including only patients with potentially curable colorectal cancer. [II] Another definition of clinical success was used, patients who had emergency surgery for perforation were not included. [III] Stent perforation reported as 2% in the Paper. However, perforation caused by the guidewire = 2% was not included. The perforation rate was calculated among the entire study group (n = 141) although all perforations were reported in the subgroup of patients (n= 56) with acute obstruction only.

Even so, mortality after SEMS and surgery is much lower than the 21% mortality rate observed after emergency surgery for colonic obstruction in Denmark (VIII), thus supporting the beneficial effect of SEMS in acute bowel obstruction. In a short-term perspective, the survival benefit of SEMS insertion seems even more obvious in acute patients having SEMS as palliation because the 30-day mortality after emergency surgery with palliative outcome is 30% in Denmark (VIII). This discrepancy is noteworthy, especially in patients with a short life-expectancy. The perforation rate, however, requires further attention as perforation is the main contributor to mortality (188).

While the short-term outcome of SEMS as bridge to surgery or as definitive palliation seems promising, concerns have been expressed regarding the safety and efficacy of SEMS in a long-term perspective. The concerns relate to the oncological outcome in patients having SEMS as bridge to surgery, which is described in Section 6.2.6., and the occurrence of late complications requiring

re-intervention in patients on palliative chemotherapy (191,194,195). Decision-making about treatment is particularly challenging in patients with incurable obstruction not presenting acutely in whom the consequences of late complications like perforation, migration and re-obstruction caused by tumour in-growth or overgrowth, and faecal impaction should be considered. The increasing efficacy of palliative chemotherapy prolongs the life of such patients. Thus, the time requirements for stent patency also increase. However, numerous (retrospective) single-centre studies have reported comparable long-term results of SEMS and surgery in incurable colorectal cancer (198-200). Nevertheless, the SEMS modality in patients with non-acute incurable obstruction needs further evaluation regarding its long-term outcome.

## 6.2. LONG-TERM SURVIVAL FROM COLORECTAL CANER
### 6.2.1. Overall
Long-term survival from colonic and rectal cancer in Denmark has been rising steadily for more than 30 years (I, II) (201,202). From the period 1977-1982 to the period 1995-1999, the 5-year relative survival improved by 9% in both colonic and rectal cancer according to data from the Danish Cancer Registry (I), **Table 16**.

**Table 16**

5-year relative survival of 69,562 Danish colorectal cancer patients according to tumour site, 1977-1999 (% (95% CI))

| Year of diagnosis | 1977-1982 | 1983-1988 | 1989-1994 | 1995-1999 |
|---|---|---|---|---|
| Colon | 38.1 | 40.7 | 44.7 | 46.9 |
| | (37.0-39.3) | (39.6-41.8) | (43.6-45.9) | (45.3-48.5) |
| Rectum | 37.3 | 39.6 | 42.8 | 46.6 |
| | (35.9-38.8) | (38.2-41.1) | (41.3-44.3) | (44.4-48.8) |

The improvement was mainly seen within the first 6 months after diagnosis after which the survival curves for the different time periods became almost parallel (I). The oncological effect of colo-rectal cancer surgery is not expected to manifest itself until after 1-3 years. We therefore cannot conclude that a significant im-provement of the oncological treatment succeeded in the period investigated here. Actually, surgery which is the main oncological treatment modality in colorectal cancer was not refined in the period 1977-1999, apart from the introduction of the TME tech-nique in rectal cancer in the late 1990s.

The most recent survival analyses from the Danish Cancer Regis-try revealed a further survival improvement in the period 2004-2006: The 5-year relative survival from colonic cancer for men and women rose to 52% (95% CI 51-54) and 57% (95% CI 55-58), respectively, and from rectal cancer to 55% (95% CI 53-57) and 57% (95% CI 55-59), respectively (202).

Thus, the overall 5-year relative survival has increased markedly from the early 1990s to the mid 2000s with a yearly increase of 0.5-1% from 1977-1999, irrespective of tumour site. A similar increase was seen for colonic cancer from 1995-1997 to 2004-2006 - a period in which the 5-year survival from rectal cancer increased even more.

The impact of the National Cancer Plan on colorectal cancer sur-vival has been analysed on the basis of data from the hospital discharge registries (II) and the Danish Cancer Registry (202,203). Analyses based on the former showed that the 1-year crude survival from colonic cancer remained constant at 65% from 1995-1999 to 2000-2004, while the 1-year crude survival from rectal cancer rose from 71% to 74% (II). A similar pattern was seen when data were corrected for age and gender. The most recent analyses based on data from the hospital discharge regis-tries, however, reveal an increase in the 1-year crude survival from colonic cancer to 69% in 2004-2006 and 70% in 2007-2009, whereas the 1-year crude survival from rectal cancer has in-creased even more to 76% in 2004-2006 and 78% in 2007-2009 (204). These unadjusted analyses also showed a minor increase in the 5-year crude survival from colonic cancer from 40% in 2001-2003 to 43% in 2004-2006 with no further increase in 2007-2009; the latter two figures were predicted (204). The corresponding figures for rectal cancer were 2001-2003 43%, 2004-2006 46% and 2007-2009 47%. Storm et al compared the age-adjusted, gender-specific relative survival from 1998-2000 to 2001-2003 and reported increasing 1-year figures for rectal cancer only, although the 3-year relative survival from colonic cancer in women also improved from 55% to 61% (203). In Storm's et al most recent analyses, no further improvements in 1-year relative survival from colonic or rectal cancer were observed when the period 2001-2003 period was compared with the 2004-2006 period; nor did they observe any major improvement in 5-year survival (202).

Women continued to have a long-term survival advantage of about 3-5% in absolute figures (I). A more favourable outcome for women has also been observed in Sweden (205) and Scotland (206), though the opposite has been reported for colonic cancer in Norvway (207). For numerous other cancer sites, survival is higher in women than in men (208).The relationship between gender and outcome is not clear. Differences in mode of presen-tation, stage distribution, tumour site, socioeconomic status, alcohol and tobacco consumption, comorbidity and use of sex steroids are some of the factors suggested to explain the gender difference in outcome (208,209).

The survival improvements in Denmark were most pronounced for rectal cancer. Bülow has recently reported a substantial in-crease in survival among Danish rectal cancer patients registered in the DCCG database (110). Bülow used periodic monitoring and found that the 5-year relative survival rates were 46% in 1994 and estimated that the rates would reach 62% in 2006. Interestingly, survival from rectal cancer in Denmark has in the 2000s just sur-passed that of colonic cancer (202,204). A similar trend has been reported by the Swedish Cancer Registry based on 5-year relative survival from 1995-1999: colonic cancer 57.2% and rectal cancer 57.6% (205), but also by the Norwegian Cancer Registry (210) and for southern Netherlands (134) and Scotland (206). The beneficial regimen of preoperative radiotherapy and TME surgery in pa-tients with resectable rectal cancer was introduced in a few hos-pitals in Sweden in the early 1990s. It was implemented nation-wide in 1995 which was about 5 years before its introduction in Denmark. This approach also meant that surgery was being per-formed by fewer, better trained surgeons. Other beneficial treatment-related changes, such as preoperative MRI, decision-making in MDT, etc., have been implemented among others in Sweden and Norway. They have produced significant improve-ment in rectal cancer survival in these countries (211-213) as well as in Denmark (110).

The survival differences between Denmark and the other Nordic countries remain striking. Survival rates for Danish patients diag-nosed in 1990-1994 was in line with those reported for Eastern

Europe and the UK (214). Recent 5-year relative survival rates are available from the NORDCAN database for patients diagnosed in 1999-2003. Survival in this most recent period was calculated using the hybrid analysis methods by which country-specific mortality was used to calculate expected survival, **Table 17**. The Danish figures were 6-10% lower in absolute figures than all figures from Norway, Sweden and Finland. Comparing the survival figures with those of the period 1989-1993, no conspicuous large-scale differences in absolute increases in percentage points across the Nordic countries, including Denmark, were observed. However, survival from colonic cancer improved at bit more in Finland as did survival from rectal cancer in Denmark and Finland, **Table 17**. The survival deficit in Denmark is confirmed by the most recent relative survival estimates in Denmark, Norway, Sweden, UK, Canada and Australia calculated by the International Cancer Benchmarking Partnership based on patients diagnosed during 1997-2007 and registered in population-based cancer registries (215).

Thus, the inferior prognosis of rectal cancer in Denmark as compared with the rest of the North seems to be shrinking marginally. For colonic cancer, Denmark is not doing more badly than the other countries.

The reasons for this survival variation in the North have been studied using sophisticated analyses of data from NORDCAN in which the age-adjusted excess mortality was calculated. In 2007, Engholm demonstrated that Danish colorectal cancer patients have a higher excess mortality during the first 6 months after diagnosis than patients in Norway, Sweden and Finland (77). A similar finding was reported by the EUROCARE study in 1995 for colon cancer (1) and, recently, for rectal cancer by Folkesson (114) who also observed a different the stage distribution between countries and, after adjusting for stage, the excess mortality among Danes disappeared after 6 months. This observation parallels our findings of at least twice as high 30-day mortality rates in Denmark as in those other countries. In line with this, Morris et al. (217) have just published the results of a comparison of survival from colorectal cancer in England, Norway and Sweden. They reported that the inferior survival from colonic cancer in England was due to excess mortality in the first 3 months, especially among the elderly. In rectal cancer, the excess mortality remained until 2 years after diagnosis. The authors suggested that this may be indicative of suboptimal perioperative care.

Thus, to improve long-term survival, Denmark ought to focus on reducing the high postoperative mortality. Interestingly, based on a French population-based study, Mitry calculated that a reduction of the 30-day mortality from 18% to 8% had led to a relative improvement in the 5-year survival of 27.5% (116).

### 6.2.2. Elderly patients

It is well-established that crude survival from colorectal cancer declines with increasing age (118,138), which is very apparent among the elderly aged >75 years (96,132,133,204). Crude survival may not be an appropriate measure of outcome because life expectancy decreases with advancing age. Cancer-specific survival would be a more appropriate measure. In fact, cancer-specific survival has consistently been reported to be similar among elderly and their younger counterparts (131,146,218,219). In Sweden, a lower cancer-specific survival among elderly patients aged >80 years has been reported, although the observation may be biased by improper information on the cause of death that entailed an overestimation of cancer deaths in the elderly (132). However, the relationship between age and outcome is complex and may be confounded by differences in stage, tumour site, comorbidity and type of treatment, among others (220). The Danish 5-year relative survival estimates for the period 1995-1999 are shown in **Table 18**; the relative survival of those aged >80 years was lower than that of younger patients (III). However, the elderly aged >75 years, in particular, had experienced a marked 13-16% increase in relative survival from the period 1977-1982 to the period 1995-1999 as compared to 7% among their younger counterparts. These improvements in survival were accompanied by an increasing rate of curative surgery and decreasing 30-day mortality among the elderly (III).

**Table 18**

**Relative survival of 69,562 Danish colorectal cancer patients by age, 1995-1999 (% (95% CI))**

| Age group | ≤ 60 | 61-75 | 76-80 | 81-85 | 86+ |
|---|---|---|---|---|---|
| Relative 5-year survival | 49 (46-51) | 47 (46-49) | 47 (43-50) | 43 (39-48) | 39 (33-45) |

Thus, although survival from colorectal cancer remains age-related with declining survival with advancing age, the gap between survival of younger and elderly patients has decreased markedly.

**Table 17**

**5-year age-standardised relative survival of colonic and anorectal and anal cancer patients according to tumour site based on data from NORD-CAN, 1999-2003 (% (95% CI)) and absolute increases (percentage points) since 1989-1993 (216)**

| | | Denmark | | Norway | | Sweden | | Finland | |
|---|---|---|---|---|---|---|---|---|---|
| Colon | Men | 49 (47-50) | +6% | 55 (54-57) | +6% | 56 (55-57) | +4% | 59 (57-61) | +8% |
| | Women | 52 (51-53) | +6% | 59 (57-60) | +6% | 60 (59-61) | +6% | 62 (61-64) | +9% |
| Rectum+ anus | Men | 49 (48-51) | +8% | 57 (56-59) | +9% | 57 (56-58) | +6% | 57 (55-59) | +11% |
| | Women | 53 (51-54) | +10% | 63 (61-65) | +6% | 62 (61-64) | +7% | 60 (58-62) | +10% |

**Figure 7**
**Temporal trends in relative survival of elderly colorectal cancer patients aged >76 years and 61-75 years, 1977-1997**
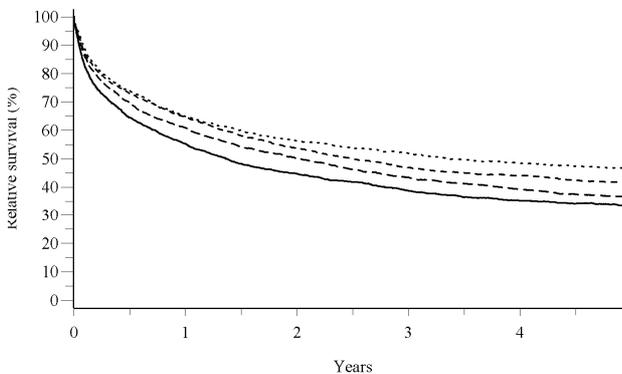


n = 12,181 patients aged 76-80 years
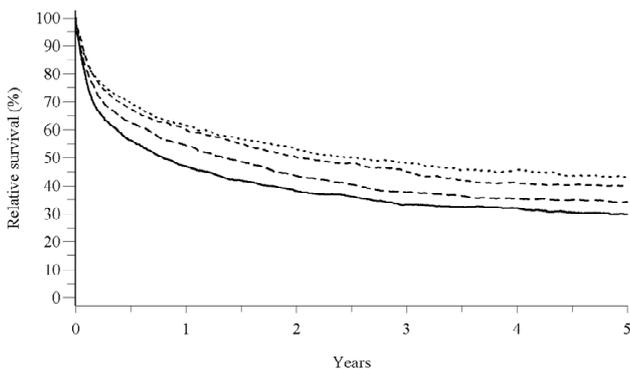


n = 9,283 patients aged 81-85 years



n = 6,428 patients aged 86+ years



Period ——— 1977-1982   — — 1983-1988   – – 1989-1994   · · · 1995-1999

n = 29,898 patients aged 61-75 years

The temporal trends in relative survival among the elderly and those aged 61-75 years are depicted in **Figure 7**. A comparison of the survival curves reveals that mortality from colorectal cancer, as compared to other caus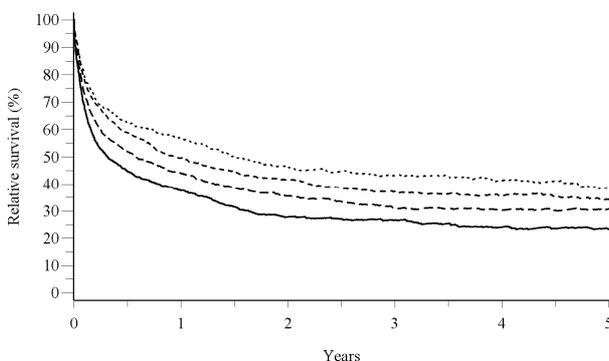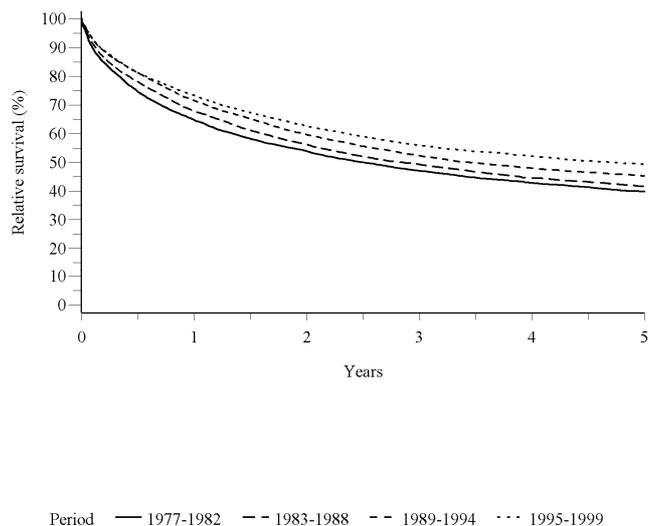es, was excessive in the elderly during the first two years, after which this over-mortality levelled off. Similar trends appear in recent relative survival curves for colonic and rectal cancer patients aged ≥70 years from the Netherlands (134). Danish patients aged >75 years had a slightly lower relative survival from colorectal cancer two or more years after diagnosis than did their younger counterparts. Competing causes of death in the elderly probably contribute to this finding. On the other hand, survival from colorectal cancer in elderly patients was fair if they survived the first two years, particular the first six months. This finding is consistent with a review of population-based studies that concluded that those elderly who survive the first year have a prognosis similar to that of younger patients (145). In line with the Danish results, the EUROCARE study (118) reported that survival differences between younger and older patients were larger one than five years after diagnosis. In that study, however, cancer stage at presentation was suggested to be the main factor contributing to excess mortality. The most recent EUROCARE-4 study (221) noticed that the gap between the relative survival from colonic cancer in middle-aged (55-69 years) and elderly patients (70-84 years) widened in the period 1988-1999 because survival improved more among the former; this observation conflicts with the Danish results.

Conflicting results on outcome of TME surgery for rectal cancer in elderly have emerged (96,140). A Norwegian study reported no difference in the relative survival of elderly rectal cancer patients treated with a curative intent and their younger counterparts. The authors concluded that selected elderly may benefit from TME surgery without radiotherapy (96). In Sweden, the 5-year relative survival from rectal cancer was slightly lower among elderly aged ≥75 years than among their younger counterparts, 64% vs. 68%, respectively, (133). Although the Swedish elderly who had abminoperineal excision received preoperative radiotherapy less frequently, 47% vs. 82%, their rate of local recurrence was comparable to that of the younger patients. The lower rate of radiotherapy could therefore not entirely explain their inferior survival. Results from the Dutch TME study on highly

**Table 19**

**Overall survival and adjusted relative mortality rates for 13,190 patients with colonic and rectal cancer from 1995 through 2006**

| Year of diagnosis | 1995-1997 | 1998-2000 | 2001-2003 | 2004-2006 |
|---|---|---|---|---|
| Colonic cancer | | | | |
|   1-year overall survival (95% CI) | | | | |
|     Charlson score 0 | 69% (66-71%) | 70% (68-73%) | 75% (72-77%) | 75% (73-78%) |
|     Charlson score 1-2 | 60% (55-64%) | 62% (58-66%) | 63% (59-66%) | 69% (65-72%) |
|     Charlson score 3+ | 53% (43-61%) | 51% (43-59%) | 44% (37-51%) | 58% (51-65%) |
|   1-year relative mortality rate[1] (95% CI) | | | | |
|     Charlson score 0 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
|     Charlson score 1-2 | 1.3 (1.1-1.5) | 1.2 (1.0-1.4) | 1.5 (1.2-1.8) | 1.2 (1.0-1.5) |
|     Charlson score 3+ | 1.7 (1.3-2.3) | 1.9 (1.5-2.4) | 2.5 (2.0-3.2) | 1.8 (1.4-2.3) |
| Rectal cancer | | | | |
|   1-year overall survival (95% CI) | | | | |
|     Charlson score 0 | 75% (72-78%) | 78% (75-81%) | 81% (78-84%) | 83% (80-86%) |
|     Charlson score 1-2 | 65% (60-70%) | 67% (61-71%) | 69% (64-74%) | 71% (66-76%) |
|     Charlson score 3+ | 50% (37-61%) | 54% (44-64%) | 47% (37-57%) | 50% (39-59%) |
|   1-year relative mortality rate[1] (95% CI) | | | | |
|     Charlson score 0 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
|     Charlson score 1-2 | 1.4 (1.1-1.8) | 1.5 (1.2-1.9) | 1.6 (1.3-2.1) | 1.5 (1.1-2.0) |
|     Charlson score 3+ | 2.2 (1.5-3.2) | 2.3 (1.7-3.3) | 3.1 (2.3-4.2) | 3.2 (2.3-4.4) |

[1]Adjusted for age, gender, time, and treatment policy

selected elderly patients showed, however, that the addition of short-course radiotherapy to TME surgery was associated with improved cancer-specific survival, but not with overall survival. This latter was ascribed to an increase in non-cancer-related mortality, especially within the first 6 months (140). However, analysis of the Ducth rectal cancer patients from the most recent years (i.e., data up until 2006) contradicts the observation of no increase in overall survial: a modest improvement has now been observed in the 5-year relative survival of also elderly rectal cancer patients in the Netherlands (134).

The beneficial effect of adjuvant chemotherapy for resected colonic cancer in patients ≥70 years finds support in reviewed reports (222,223) and in the fact that elderly enjoy the same potential gains from palliative chemotherapy as their younger counterparts. However, the evidence concerning toxicity remains inconclusive (223). The proportion of elderly in Denmark receiving adjuvant and palliative chemotherapy has not yet been reported. However, in the Netherlands, this proportion is extremely low, but rising (224): Only 5% of the elderly aged ≥80 years received adjuvant chemotherapy and 10% received palliative chemotherapy in 2005-2007 in the southern part of the Netherlands (134). Dutch national data on colonic cancer patients aged ≥75 years diagnosed in 2004-2006 reveal the use of adjuvant chemotherapy among 19% of stage III patients and among 40% of stage IV patients (224).

### 6.2.3. The impact of comorbidity
Comorbidity adversely impacts long-term survival among Danish colorectal cancer patients (VI). As shown in **Table 19**, the overall 1-year survival from colonic and rectal cancer decreased by an increasing Charlson Comorbidity score for every 3-year period during the study period from 1995 to 2006. Similarly, the 5-year survival from colonic cancer in 1998-2000 was 43% in non-comorbid patients and 20% in patients with severe comorbidity. The corresponding figures in rectal cancer were 46% vs. 21%. The mortality rate ratios (MRR) (i.e., hazard ratios computed by re-

gression analysis where mortality rates are compared among the comorbidity groups and adjusted for age, gender, time period and treatment policy) confirmed the negative impact of comorbidity on survival, **Table 19**. Comorbidity had an even stronger impact in rectal cancer than in colonic cancer as revealed by higher MRRs in rectal cancer. In the period 2004-2006, the risk of dying within 1 year among rectal cancer patients with severe comorbidity was about trice that of non-comorbid patients. Increasing MRRs by increasing comorbidity was also observed in the subgroup of patients who underwent the most aggressive treatment, i.e., resection.

Thus, the poorer outcome among comorbid patients could not be caused only by the use of suboptimal treatment. In other words, mortality may be attributed to comorbidity in a majority of co-morbid colorectal cancer patients.

Multivariate analysis of the causes of death in colorectal cancer patients has shown that patients with a Charlson Comorbidity score 3+ had almost a four-fold increased risk of dying of non-cancer-related causes compared with patients with a Charlson Comorbidity score 0-2 (225).

On the other hand, a large fraction of patients with severe co-morbidity may die with, rather than from, their colorectal cancer due to the low surgical resection rate among Danish patients with severe comorbidity, Section 6.1.3. Similarly, US population-based studies have concluded that comorbidity has a stronger effect on survival among patients with early-stage cancer, i.e., longer life expectancy, than on patients with late-stage disease (226,227). The Danish results with decreasing long-term survival by increasing level of comorbidity are in line with findings from other populations. A number of studies have thus concluded that comorbidity has an independent adverse effect on survival after adjustment for age, sex, tumour stage, choice of treatment and deprivation, among others (121,148,149,227-229). Social inequality in survival has been documented among Danish colorectal cancer patients, i.e., patients with a low SES have a poorer sur-

vival than patients with a high SES. However, this socioeconomic difference was mainly attributed to differences in comorbidity level, and to some extent also to lifestyle (230).

Thus, comorbidity impacts survival heavily.
The mechanism through which colorectal cancer survival is affected by comorbidity seems to be complex. Lemmens et al. reported that cardiovascular disease, chronic obstructive pulmonary disease (COPD) and the combination of hypertension and diabetes were associated with worse survival from colorectal cancer (148). A more recent study on patients who had resectional surgery only found that cardiovascular disease, COPD and diabetes all had an independent prognostic effects on the overall survival from colonic cancer. However, cardiovascular disease and COPD had an independent prognostic effect on survival from rectal cancer (149). Furthermore, congestive heart failure, cerebrovascular disease, dementia, hemi/paraplegia, renal disease and moderate or severe liver disease have all been found to be associated with an increased risk of death within the first year after the cancer diagnosis (229). Some combinations of comorbidity, such as diabetes mellitus and congestive heart failure, have been shown to affect survival more than others, such as diabetes and COPD (228).
Another reason for the observed disparity in survival between comorbid and non-comorbid patients lies in the differences in treatments offered as described in Section 6.1.3. However, data are conflicting and probably influenced by selection bias: comorbid patients in good performance are more likely to receive a treatment offer and to receive treatment than patients displaying more inferior performance. Concerning adjuvant chemotherapy in stage III colonic cancer, patients with (severe) comorbidity have been found to suffer less excess overall mortality if they were offered chemotherapy (150,231). However, comorbidity has also been reported to worsen cancer survival independently of cancer treatment and, suboptimal cancer treatment thus cannot (fully) account for the observed differences in survival between patients with and without comorbidity (149,228).

### 6.2.4. Caseload and surgical speciality
The literature overwhelmingly reports a volume-specialty-outcome relationship regarding survival in complex surgical oncology such as pancreaticoduodenectomy (164,165) and oesophageal resection (165). Data on colonic and rectal cancer surgery have been more inconsistent.

A review of the literature from 1992 through June 2004 on studies including at least 500 patients reporting the long-term outcome of surgery for colorectal cancer identified 34 studies (V). The interpretation of the association between the volume-specialty variables and overall survival for colonic cancer, rectal cancer and colorectal cancer combined based on these studies is listed in **Table 20** (V).
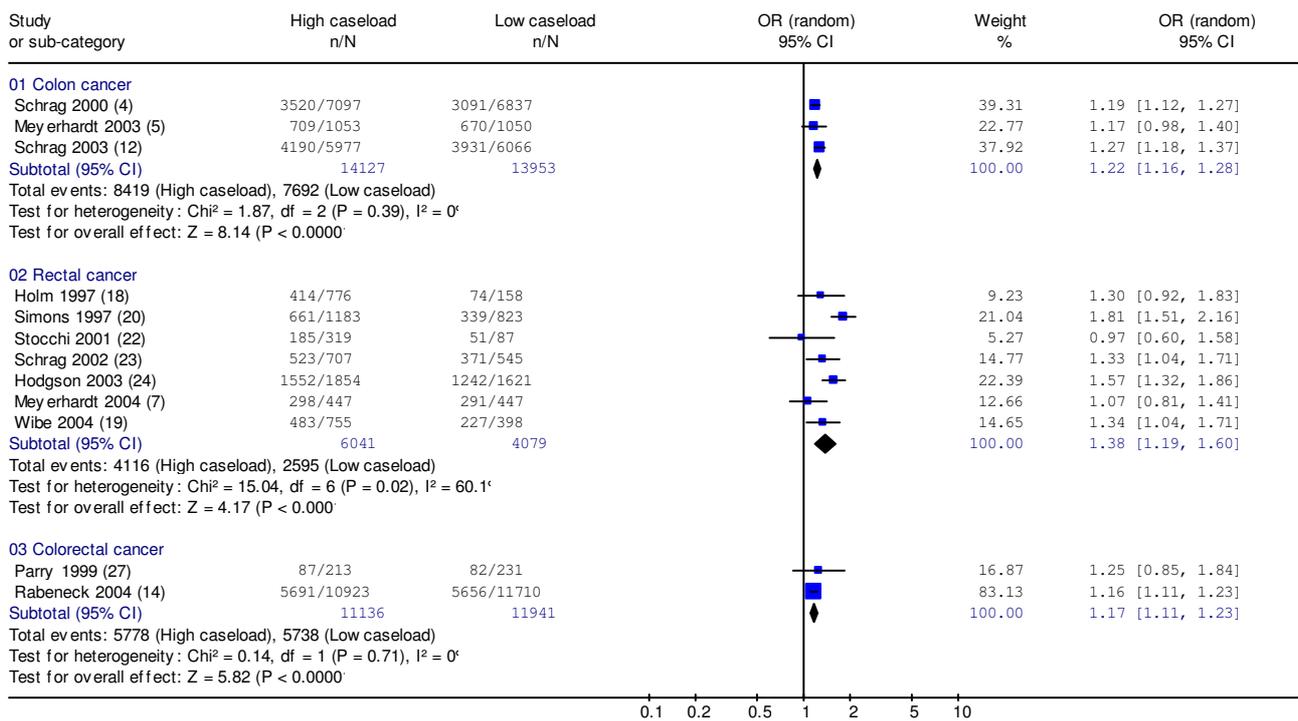A high hospital caseload was significantly associated with improved overall survival from colonic cancer, OR 1.22 (1.16 -1.28), and from rectal cancer, OR 1.38 (1.19 -1.60), **Figure 9**.
In case-mix-adjusted analysis, surgeon caseload was not significantly associated with overall survival from colonic cancer in contrast to the unadjusted analyses as shown in **Figure 10**. However, the cut-points for low and high caseload were extremely low, <2 operations per year vs. >4 operations per year (232). Similarly, in the rectal cancer studies, very low cut-points for surgeon caseload were used.
Studies on surgeons' education were too heterogeneous to allow a meta-analysis. However, for all three groups, i.e., colonic cancer, rectal cancer and colorectal cancer combined, specialists outperformed non-specialists and sub-specialists like colorectal surgeons outperformed general surgeons by achieving better overall survival (and cancer-free survival) of their patients.
Thus, long-term survival from colonic and rectal cancer improved significantly with increasing hospital caseload and the surgeon's education.
The review failed to find a positive effect of surgeon caseload on survival, which contradicts observations in other technically challenging surgical procedures such as coronary artery bypass grafting (165). Besides the methodological problems due to unrealistically low cut-points for surgeon caseload, it must be emphasized that a high hospital caseload may be a proxy for other factors that significantly influence outcome, such as assistance from other specialities, clinical decision-making in multidisciplinary teams, feedback on treatment and training exercise, among others. Furthermore, the variability in outcome may be rooted in surgeon training and experience and not in surgeon caseload. Because of their acquired knowledge and technical skill in addition to their collective team spirit, sub-specialized surgeons who are likely to be employed at high-volume hospitals may not need a high caseload themselves to maintain good long-term survival of their patients.
All these factors, i.e., hospital caseload, surgeon caseload, as well as surgeon specialty and experience, interact in the volume-specialty-outcome relationship. The interaction between hospital caseload and surgeon caseload is complex and its effect may depend on the outcome of interest. For instance, hospital caseload may affect surgeon outcome such as postoperative mortality because of the associated hospital infrastructure, as described in Section 6.1.5. Thus, any postoperative complications can usually be managed at the expert level in high-volume hospitals; and rectal cancer surgeons are usually specialized, work in hospitals with a high caseload, have high caseload themselves and are more experienced. Surgeon caseload and specialization

**Table 20**

**Strength of evidence for an association between selected variables and survival**

[I] Based on one study. [II] Based on two studies. [III] Based on studies not stratified for tumour origin. NA: not applicable

| Survival (No. of studies) | Hospital caseload | Surgeon's caseload | Surgeon's education | Surgeon's experience | Type of hospital |
|---|---|---|---|---|---|
| Colonic cancer, n = 8 | Strong | No [I] | Strong [II] | NA | Weak[I] |
| Rectal cancer, n = 12 | Strong | No | Strong [I] | Strong [I] | Weak |
| Colorectal cancer[III], n = 10 | Weak | No | Strong | No [I] | No [I] |

| Study<br>or sub-category | High caseload<br>n/N | Low caseload<br>n/N | OR (random)<br>95% CI | Weight<br>% | OR (random)<br>95% CI |
|---|---|---|---|---|---|
| **01 Colon cancer** | | | | | |
| Schrag 2000 (4) | 3520/7097 | 3091/6837 | | 39.31 | 1.19 [1.12, 1.27] |
| Meyerhardt 2003 (5) | 709/1053 | 670/1050 | | 22.77 | 1.17 [0.98, 1.40] |
| Schrag 2003 (12) | 4190/5977 | 3931/6066 | | 37.92 | 1.27 [1.18, 1.37] |
| **Subtotal (95% CI)** | **14127** | **13953** | | **100.00** | **1.22 [1.16, 1.28]** |
| Total events: 8419 (High caseload), 7692 (Low caseload) | | | | | |
| Test for heterogeneity: Chi² = 1.87, df = 2 (P = 0.39), I² = 0% | | | | | |
| Test for overall effect: Z = 8.14 (P < 0.00001) | | | | | |
| **02 Rectal cancer** | | | | | |
| Holm 1997 (18) | 414/776 | 74/158 | | 9.23 | 1.30 [0.92, 1.83] |
| Simons 1997 (20) | 661/1183 | 339/823 | | 21.04 | 1.81 [1.51, 2.16] |
| Stocchi 2001 (22) | 185/319 | 51/87 | | 5.27 | 0.97 [0.60, 1.58] |
| Schrag 2002 (23) | 523/707 | 371/545 | | 14.77 | 1.33 [1.04, 1.71] |
| Hodgson 2003 (24) | 1552/1854 | 1242/1621 | | 22.39 | 1.57 [1.32, 1.86] |
| Meyerhardt 2004 (7) | 298/447 | 291/447 | | 12.66 | 1.07 [0.81, 1.41] |
| Wibe 2004 (19) | 483/755 | 227/398 | | 14.65 | 1.34 [1.04, 1.71] |
| **Subtotal (95% CI)** | **6041** | **4079** | | **100.00** | **1.38 [1.19, 1.60]** |
| Total events: 4116 (High caseload), 2595 (Low caseload) | | | | | |
| Test for heterogeneity: Chi² = 15.04, df = 6 (P = 0.02), I² = 60.1% | | | | | |
| Test for overall effect: Z = 4.17 (P < 0.0001) | | | | | |
| **03 Colorectal cancer** | | | | | |
| Parry 1999 (27) | 87/213 | 82/231 | | 16.87 | 1.25 [0.85, 1.84] |
| Rabeneck 2004 (14) | 5691/10923 | 5656/11710 | | 83.13 | 1.16 [1.11, 1.23] |
| **Subtotal (95% CI)** | **11136** | **11941** | | **100.00** | **1.17 [1.11, 1.23]** |
| Total events: 5778 (High caseload), 5738 (Low caseload) | | | | | |
| Test for heterogeneity: Chi² = 0.14, df = 1 (P = 0.71), I² = 0% | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | |

0.1  0.2  0.5  1  2  5  10

**Figure 9**
**Hospital caseload and overall survival in colorectal cancer surgery. Forest plot of reviewed studies stratified for tumour location (colonic, rectal, colorectal). Citations numbered as in (V).**

may therefore affect hospital outcome such as survival from rectal cancer simply because of the surgeon's own dedicated interest in the field. The simultaneous effect of the hospital's and the surgeon's caseload has been examined in rectal cancer. It appeared that variation in outcome was attributable more to

surgeon caseload than to hospital caseload (233).
Several recent reviews confirm the positive volume-outcome associations, **Table 20** (166-168), although that of Gruen (167) did not document a relationship between hospital caseload and survival from rectal cancer. A recent review of rectal cancer stud-

| Study<br>or sub-category | High caseload<br>n/N | Low caseload<br>n/N | OR (random)<br>95% CI | Weight<br>% | OR (random)<br>95% CI |
|---|---|---|---|---|---|
| **01 Colon cancer** | | | | | |
| Schrag 2003 (12) | 4130/5960 | 4150/6444 | | 100.00 | 1.25 [1.16, 1.34] |
| **Subtotal (95% CI)** | **5960** | **6444** | | **100.00** | **1.25 [1.16, 1.34]** |
| Total events: 4130 (High caseload), 4150 (Low caseload) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 5.78 (P < 0.00001) | | | | | |
| **02 Rectal cancer** | | | | | |
| Holm 1997 (18) | 186/335 | 532/1037 | | 32.08 | 1.18 [0.93, 1.52] |
| Hermanek 1999 (9) | 272/454 | 85/140 | | 18.06 | 0.97 [0.66, 1.42] |
| Stocchi 2001 (22) | 68/121 | 330/550 | | 17.39 | 0.86 [0.57, 1.27] |
| Schrag 2002 (23) | 524/689 | 386/585 | | 32.47 | 1.64 [1.28, 2.09] |
| **Subtotal (95% CI)** | **1599** | **2312** | | **100.00** | **1.16 [0.88, 1.54]** |
| Total events: 1050 (High caseload), 1333 (Low caseload) | | | | | |
| Test for heterogeneity: Chi² = 10.02, df = 3 (P = 0.02), I² = 70.0% | | | | | |
| Test for overall effect: Z = 1.04 (P = 0.30) | | | | | |
| **03 Colorectal cancer** | | | | | |
| Parry 1999 (27) | 73/151 | 53/153 | | 26.81 | 1.77 [1.11, 2.80] |
| McArdle 2004 (6) | 430/751 | 353/665 | | 73.19 | 1.18 [0.96, 1.46] |
| **Subtotal (95% CI)** | **902** | **818** | | **100.00** | **1.37 [0.94, 1.99]** |
| Total events: 503 (High caseload), 406 (Low caseload) | | | | | |
| Test for heterogeneity: Chi² = 2.39, df = 1 (P = 0.12), I² = 58.2% | | | | | |
| Test for overall effect: Z = 1.63 (P = 0.10) | | | | | |

0.1  0.2  0.5  1  2  5  10

**Figure 10**
**Surgeon's caseload and overall survival in colorectal cancer surgery. Forest plot of reviewed studies stratified for tumour location (colonic, rectal, colorectal). Citations numbered as in (V).**

ies published from 1997 to 2009 concluded otherwise (170). The review found no evidence of an association between high hospital caseload and improved survival. Instead, it reported that high surgeon caseload and in particular the availability of a specialist colorectal surgeon was associated with improved survival. However, this review did not include all the studies reviewed by Iversen et al. (V) and, most importantly, it performed no meta-analysis, but based its conclusions on the sum of significant and non-significant studies only; i.e., it employed the same method as Gruen (167). Another recent meta-analysis on rectal cancer, but based on two studies only, reported a significant association between high surgeon volume and improved survival (169).

As described in Section 6.1.5., several methodological issues and confounding factors hinder definite conclusions regarding the volume-specialty-outcome relationship, but the data give grounds for a number of assumptions. The quality of surgery has not been evaluated in such studies and a big concern in the interpretation of the volume-specialty-outcome relationship in rectal cancer is that the prognostic superiority of the TME technique was not used in all of the previous studies.

The reported relationship between hospital/surgeon caseload and survival in the most recent population-based studies (in which adjustment for case-mix was performed) is shown in **Table 21**. These recent studies confirm a volume-outcome effect regarding hospital caseload.

Furthermore, evidence demonstrating an effect of surgeon caseload in colonic cancer has recently appeared. However, in several of these studies, the cut-points were rather low; for instance in the Swedish study by Brännström (237), the median surgeon caseload for colonic cancer was 7 (range 0-15) operations per year and for rectal cancer 9 (range 0-18) per year, i.e., one operation every month or every second month only. In the Danish rectal cancer study, a high hospital caseload was defined as more than 30 operations per year corresponding to about one operation per week (10). Such low caseloads make it difficult to detect a difference between the studies.

In a populations-based study from the northern Region of England, survival rates from colonic cancer were significantly better for surgeons with a high caseload after adjustment had been made for case-mix and hospital volume, whereas in rectal cancer such an association was evident for hospitals with high caseload after adjustment for surgeon caseload (99).

Thus, evidence is growing that also surgeon caseload has an impact on long-term survival – and it may even be greater than that of hospital volume.

Considering that the management of colorectal cancer in the Netherlands and Denmark should be at the same level, it is thought-provoking that very recent volume-outcome studies based on TME surgery from the Netherlands convincingly documented the inferior survival of early-stage rectal cancer (T1M0) patients treated at hospitals where less than 25 patients per year underwent surgery compared with hospitals at which more than 50 patients were treated per year (136). Obviously, early-stage cancer patients should benefit most from treatment because of their long life-expectancy per se. For colonic cancer treated with an adjuvant chemotherapy regimen like that used in Denmark, the Dutch survival rates were significantly poorer at hospitals treating less than 50 patients per year than at hospitals treating more than 50 patients per year (135). In comparison, four Danish surgical departments treated less than 50 colonic cancer patients per year in 2008, and one-third of the 24 departments treated less than 75 patients (17).

**Table 21**

**Survival: Volume-outcome association in recent population-based studies**

| Survival | Colonic cancer | | Rectal cancer | |
|---|---|---|---|---|
| | Hospital caseload | Surgeon's caseload | Hospital caseload | Surgeon's caseload |
| Engel 2005 (234) | | | - | NA |
| Harling 2005 (10) | | | - | NA |
| Renzulli 2006 (235) | + | + | + | + |
| Rogers[I] 2006 (172) | + | + | + | + |
| Simunovic 2006 (173) | - | NA | | |
| Birkemeyer 2007 (236) | + | NA | | |
| Morris[II] 2007 (175) | NA | + | | |
| Billimoria 2008 (176) | + | NA | + | NA |
| Kressner 2009 (177) | | | - | NA |
| Brännström 2010 (237) | NA | - | NA | - |
| Borowski 2010 (99) | - | + | + | - |
| Elferink 2010 (135) | + | NA | | |
| Elferink 2010 (136) | | | +[III] | NA |

- indicates lack of a positive association (not a negative association). [I] Analysis not stratified for tumour origin. [II] Included curatively treated stage II colonic cancer only. [III] For T1M0 tumours only

Interestingly, a recent US study reported that colonic cancer patients had a 12% higher risk of death within 5 years if they had been treated at low volume hospitals (<42 patients per year) than if they had been treated at high volume hospitals (>125 patients per year) (176). They also found that if all colonic cancer patients were treated at such high volume hospitals, a tremendous number of number of deaths (2,700 per year in the US) could be avoided simply because of the high incidence of colonic cancer in combination with the large proportion that die within 5 years.

Thus, compelling evidence demonstrates that the long-term survival from colorectal cancer depends on the hospital caseload, surgeon caseload and surgeon specialty. Unfortunately, the available literature does not allow us to draw more precise conclusions.

### 6.2.5. The significance of therapeutic delay

Delay is inherently inevitable in the diagnostic pathway of symptomatic colorectal cancer. Diagnostic delay can be categorized as shown in **Figure 3**. The sum of delay in primary health care and hospital delay is 'provider delay' and the sum of all delays is termed 'total therapeutic delay'. The definitions of delay vary,

however, across studies which makes comparison between studies troublesome (238,239). Methodological issues related to for instance the reliability and validity of patient delay measures must also be considered when studying the impact on delay (240)
A Danish population-based study on 2,212 cancer patients reported that the median patient delay was 21 days (interquartile range (i.q.r.) 7-56) and the median total delay 98 days (i.q.r. 57-168) (32). Another Danish population-based study on 743 colorectal cancer patients, diagnosed during 2001 through mid 2002, reported delays as shown in **Table 22** (241).
Patient delay and delay in secondary health care were the major contributors to total delay. However, the 2-week waiting time guarantee from diagnosis to treatment issued in 2001 was only met for 65% of elective colonic cancer patients and 47% of rectal cancer patients (241).
The impact of delay on tumour stage at the time of colorectal cancer diagnosis has been studied by Korsgaard et al (242), among others. They found that a total therapeutic delay >60 days was associated with a relative risk of 1.9 (95% CI 1.1-3.1) of having advanced disease (defined as stage III or IV) in rectal cancer, whereas delay seemingly did not influence the stage distribution in colonic cancer. A recent review concluded similarly for rectal cancer with long delay being associated with advanced stage, while the opposite was observed in colonic cancer, i.e., a long delay was associated with earlier stage, although none of the observations were statistically significant in the meta-analyses (243). The most recent population-based observational study of 272 colorectal cancer patients from Northern Holland found no association between total therapeutic delay and stage when analysing colonic and rectal cancer together, but the median total therapeutic delay of 164 days was longer than in Denmark (244).
In line with the Danish observations, delay I n Holland was longer in rectal cancer than in colonic cancer (209).
The impact of delay on colorectal cancer survival has been studied extensively and a recent review suggested a lack of association between delay and survival (238). This relationship was re-analyzed in the study cohort by Korsgaard et al. after a mean follow-up period of 3.49 years (95% CI: 3.32-3.66) for colonic cancer patients and 3.59 years (95% CI: 3.52-3.81) for rectal cancer patients (V). It was remarkable that only one fourth of the colonic cancer patients and one sixth of the rectal cancer patients experienced a time span below 60 days from their first symptom until initiation of treatment.
In colonic cancer, a total therapeutic delay ≥60 days had no influence on survival from colon cancer, **Figure 11**; neither in the multivariate analysis adjusted for age, sex, Charlson comorbidity score and urgency of surgery (HR = 0.96 (95% CI: 0.70-1.31)), nor in the model that also included stage.
Neither provider delay ≥60 days nor hospital delays ≥30 days or ≥60 days was significantly associated with survival in the adjusted analysis.
In rectal cancer, however, a total therapeutic delay ≥60 days was significantly associated with inferior survival from rectal cancer, HR = 1.69 (95% CI: 1.01-2.83), **Figure 11**. This negative influence on total therapeutic delay ceased, however, after inclusion of stage in the model, HR = 1.53 (95% CI: 0.91-2.59). Neither provider delay ≥60 days nor hospital delays ≥30 days or ≥60 days was associated with survival.
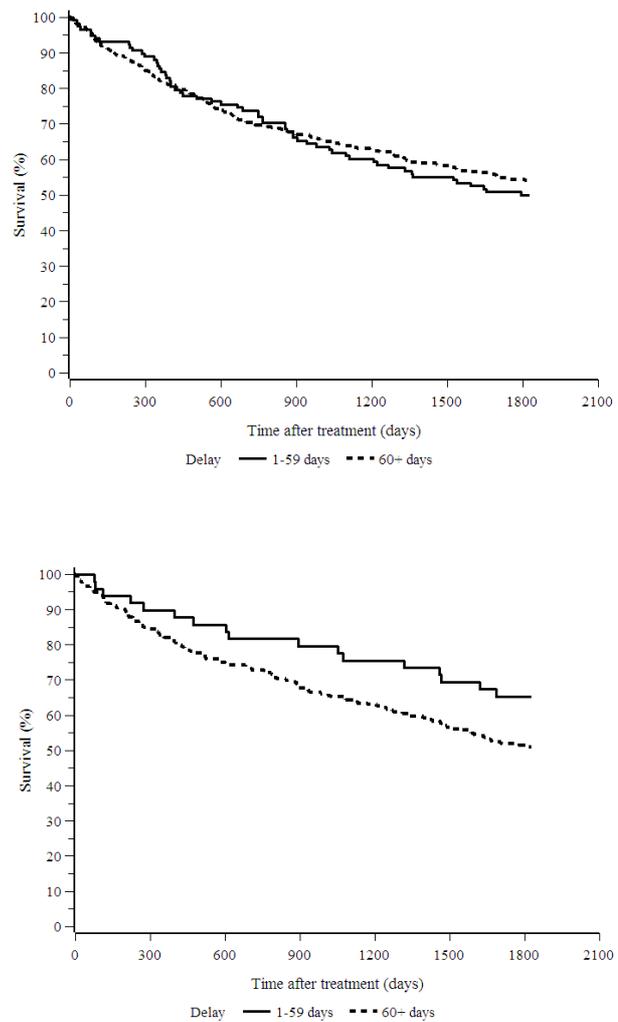




**Figure 11**
**Survival from colonic and rectal cancer according to level of total therapeutic delay, unadjusted analyses**

**Table 22**

**Median delay and interquartile range in days for Danish colorectal cancer studies (241) (X)**

| | Patient delay | Delay in primary health care | Hospital delay | Provider delay | Total therapeutic delay |
|---|---|---|---|---|---|
| Colonic cancer | 18  (i.q.r. 0-90) | 3  (i.q.r. 0-59) | 28  (i.q.r. 15-49) | 52  (i.q.r. 25-123) | 116  (i.q.r. 57-249) |
| Rectal cancer | 44  (i.q.r. 5-115) | 5  (i.q.r. 0-53) | 29  (i.q.r. 22-47) | 49  (i.q.r. 28-103) | 135  (i.q.r. 76-243) |

This recent observation of a long delay as a predictor of worse long-term survival contradicts that of previous colorectal cancer studies published in this century. Most of these studies reported no association between delay and survival (245-251), while other studies found long delay to be associated with improved survival (252) or short delay to be associated with poor survival in patients with Dukes' stage D only, as in the Dutch study (244). This is referred to as the 'waiting time paradox'. Methodological reasons may explain the diverging results as only four among seven studies reporting no association between delay and survival performed adjusted analysis (245,249-251). All of these studies included tumour stage as one of the adjustment variables. However, stage should be regarded as an intermediate step in the causal pathway between delay and survival (253) and it should therefore not be adjusted for. This is similar to the observation that screening is instrumental in detecting tumours at a less advanced stage and that screening therefore improves survival. Furthermore, stage is not a confounder as it remains unknown until after treatment. The Dutch study analysed data otherwise: they performed multivariate analysis on patients with early stage cancer and late stage cancer separately (244). The 'waiting time paradox' is known from other types of cancer as well (239) and may be caused by confounding by tumour aggressiveness, whereby less aggressive tumours may produce less aggressive symptoms and therefore longer delay and improved survival. Similarly, emergency cases combine a short delay with poor survival. A recent Danish PhD study found an u-shaped association between diagnostic delay and the 5-year mortality of colorectal cancer patients presenting with 'alarm or any serious symptoms', i.e., patients with a short delay had an increased mortality, but with decreasing levels by increasing length of short delay, and then mortality increased again with longer delay (254). Confounding due to differences in tumour aggressiveness may explain the observation of an increased mortality with a short delay, whereas the observation of increased mortality by longer delay, in parallel with that of Iversen (X), seems to be real as confounding could not explain that observation (254).

The discrepancy between colonic and rectal cancer regarding the impact of delay on prognosis is probably a reflection only of the relationship between presentation behaviour and tumour site (255). Rectal cancer patients are more likely to be delayed than colonic cancer patients and patients with vague symptoms or more common symptoms like rectal bleeding delay longer than patients with for instance pain (255). Further, colonic cancer patients are more likely to present with vague, non-specific symptoms, whereas rectal cancer patients present with more specific symptoms like rectal bleeding (15).

Thus, based on the recent Danish results that do not including stage in their analyses, a total therapeutic delay ≥60 day has a negative impact on long-term survival among rectal cancer patients, but not among colon cancer patients. Neither provider delay ≥60 days, nor hospital delays ≥30 days or ≥60 days had a prognostic impact on long-term survival from colorectal cancer. Especially patient delay and hospital delay seemed long and should be reduced. This may serve to reduce the number of patients diagnosed with late-stage disease. In the Netherlands, attention has been paid to reducing the long time interval from diagnosis to treatment, and the Dutch Cancer Society proposed in 2005 that this time should be reduced to less than 15 working days. However, an analysis of colorectal cancer patients from 2005 and 2008 revealed that the effect of these efforts has not yet been observed as this time interval has not been reduced (256).

### 6.2.6. Self-expanding metallic stents as bridge to surgery

Patients with colorectal cancer presenting as emergencies in whom emergency surgery is necessary have a poor outcome compared with patients undergoing elective surgery. Their morbidity and postoperative mortality is higher, Section 6.1.6., their resection rate is lower, their resection for cure rate is lower, and their long-term survival is poorer (111,182). Among 632 Scottish patients, the 5-year survival after emergency curative surgery was 39% compared with 71% in patients who underwent elective curative surgery (111). Other small-scale case-control studies have reported reduced long-term survival after emergency surgery compared with elective surgery (183,257). In the Danish setting and based on DCCG data, the 5-year survival from colonic cancer was 39% after acute curative surgery and 65% after elective curative surgery (16), i.e., almost similar to the Scottish results.

The use of stents as a bridge to surgery, as first described by Tejero in 1994 (40), has the potential to convert emergency surgery into an elective setting in selected patients and to allow time to perform diagnostic work-up to ensure that only patients with potentially curable cancer are offered surgical resection. Further, the risk of stoma formation is decreased because acute surgery is avoided. Issues have, however, been raised against the oncological outcome because stent-related tumour perforation is observed in at least 4% of stented patients (187-189). A further argument against this approach is that tumour cells in peripheral circulation have been detected after SEMS placement (258). Unfortunately, the literature is very sparse regarding the long-term outcome after SEMS as bridge to surgery. To date, only four studies in non-randomized designs have reported long-term outcomes (259-261) (IX), **Table 23**. One of the studies was reported in abstract form only (259).

**Table 23**

**Long-term outcomes of SEMS as bridge to surgery in patients with potentially curable colorectal cancer**

|  | Saida (259) n = 44 | Dastur (260) n = 10 | Kim (261) n = 24 [I] | Iversen (IX) n = 34 |
|---|---|---|---|---|
| Study period | 1993-2001 | 1997-2004 | 1999-2007 | 2004-2007 |
| No of days from SEMS insertion to surgery, median (range) | NA | 70 (1-223) [II] | Mean 9 (SD=6) | 35 (6-100) |
| Follow-up period, median (months) | NA | Mean 21 (SD= 25) | NA | 34 (range 0-70) |
| 3-year survival | 48% | 80% (estimated) | 44% [III] | 74% |

Analysis on patients with stage II and III only. [II] Including 12 patients. [III] 5-year survival rate

The Danish survival figures were calculated according to the intention-to-treat principle. They therefore included also patients who needed emergency surgery because of stent-related compli-

cations (IX). The 2-year and 3-year survival rates of the 34 patients with potentially curable colorectal cancer were 85% (95% CI 68-94) and 74% (95% CI 53-86), respectively. For those 30 patients who had a curative outcome, the 2-year and 3-year survival rates were 90% (95% CI 72-97) and 77% (95% CI 54-89), respectively. Half of the patients had stage III cancer.

Thus, the SEMS concept made it possible to achieve 3-year survival rates in emergency surgery reaching 75%, i.e., rates similar to those seen after elective surgery for colonic cancer with a curative outcome in Denmark (16).
The time period from SEMS placement to elective surgery has to be defined. In most studies, the median interval was 5-6 days (189), but it was much longer in the English and Danish studies, Table 23. Arguments for a long interval include the need for sufficient time for reversion and recovery of the pathophysiological mechanisms associated with bowel obstruction, the need for sufficient bowel decompression to facilitate (curative) surgery, the time required to perform diagnostic work-up, the possibility of offering neo-adjuvant chemotherapy to selected patients and need to create space on surgery lists. Arguments against a long interval include a potentially higher risk of stent-related complications requiring re-intervention like migration and perforation. One of the four patients with perforation in the Danish study could have been spared emergency surgery had elective surgery been performed 5-6 days after SEMS placement. Some have recommended that the use of SEMS as bridge to surgery in patients with potentially curable disease should only to be considered when surgery is promptly scheduled after SEMS insertion (195).

Thus, promising results in regard to curative outcome and survival may be achieved by the use of SEMS as bridge to surgery in acute bowel obstruction even though a disproportionately high perforation rates may occur as serious adverse events.


## 7. CONCLUSION

PAPER I
The overall 5-year relative survival for Danish colorectal cancer patients rose from 37.8% to 46.8% during the period 1977-1982 to 1995-1999. The observed survival improvement was caused mainly by an 8% improvement in survival within the first 6 months after diagnosis (I).

PAPER II
During 1985-2004, the crude 1-year and 5-year survival for colon and rectal cancer improved. A further improvement in 1-year survival from 71% to 74% and in the 1-year relative mortality could be identified for rectal cancer after implementation of the National Cancer Plan in 2000. Such an improvement was not observed for colon cancer (II).

PAPER III
Elderly patients, aged >75 years, experienced improvements in relative survival from colorectal cancer of 13-16% from 1977-1982 to 1995-1999. In 1995-1997, only minor differences existed in 5-year relative survival between younger (49%), middle-aged (47%) and elderly (39-47%) patients. The radical resection rate simultaneously rose markedly among elderly patients where it

was performed almost as frequently in 1995-1997 (49.2%) as in patients ≤75 years (46.7-51.4%) (III).

PAPER IV-V
Review of the literature published from 1992 through June 2004 provided evidence that (i) high hospital caseload, (ii) high surgeon's caseload, (iii) surgeon's sub-speciality and (iv) surgeon's experience were collectively associated with an improved short-term outcome after surgery for colonic cancer. Such an association could not be documented for rectal cancer due to the sparse literature on this disease (IV). Data on long-term outcome showed that a high hospital caseload was associated with an improved overall survival from colonic and rectal cancer. The surgeon's surgical sub-speciality had a positive impact on cancer-free and overall survival from colonic and rectal cancer (V).

PAPER VI
At least one-third of colorectal cancer patients suffered from comorbidity as documented in hospital discharge registries. Comorbidity had a substantial impact on survival; both 1-year and 5-year survival decreased with increasing Charlson Comorbidity Index scores. Patients with severe comorbidity may therefore die with, rather than from, their colorectal cancer. The negative impact of comorbidity was most pronounced on the outcome of rectal cancer (VI).

PAPER VII
The 30-day mortality for colorectal cancer patients operated during 1996 through 2006 exhibited no seasonal variations like those seen for some cardio-pulmonary diseases even though the majority of patients suffered from comorbidity as assessed by the ASA score. A non-significant increase was observed in July in colonic cancer and comorbid patients (VII).

PAPER VIII
The overall 30-day mortality after emergency surgery for colonic cancer in Denmark was 22.1% in the period 2001-2005. The 30-day mortality was 8.5% for those 59.2% of the patients who had an uneventful post-operative course and 39.4% for patients who developed one postoperative complication (27.8%). The strongest independent risk factor for death within 30 days after surgery was postoperative medical complications (OR = 11.7). Other risk factors were age ≥71 years, male gender, ASA grade ≥ III, palliative outcome, free or iatrogenic tumour perforation, splenectomy and intraoperative surgical adverse events (VIII).

PAPER IX
Patients with acute bowel obstruction seemed to benefit from a SEMS insertion as measured by a cumulative 30-day mortality of 2.9%, and 2-year and 3-year survival rates of 85% and 74%, respectively, i.e., figures being comparable to those achieved after elective surgery. The clinical implications of the high perforation rate of 11.8% must await further analysis in larger patient cohorts (IX).

PAPER X
Delay ≥60 days from the onset of symptoms until initiation of treatment (total therapeutic delay) was a predictor of inferior long-term survival from rectal cancer, HR = 1.69 (95% CI: 1.01-2.83). Such an association was not found for colon cancer. Provider delay ≥60 days and hospital delays ≥30 days or ≥60 days had no prognostic impact on long-term survival from colorectal cancer (X).

## 8. SUMMARY

This thesis has reported survival among Danish colorectal cancer patients over the past decades and it has explored different aspects of the inferior short-term and long-term survival of Danish patients in relation to (i) patient factors: old age and comorbidity; (ii) disease factors: prognostic factors for early death after emergency surgery; (iii) diagnostic factors: impact of diagnostic delay; (iv) treatment factors: seasonal variation in postoperative mortality and the benefit of a new approach for management of obstructive cancer; and (v) structural factors: hospital volume and surgeon characteristics.

### SHORT-TERM SURVIVAL

For colonic cancer, the 30-day relative survival rose from 86% in 1977-1982 to 90% in 1995-1999, and for rectal cancer it rose from 90% to 94% (I). Data from regional hospital discharge registries show that the overall 30-day mortality rates of colonic and rectal cancer remained stable at about 11% and 4-5%, respectively, during 1985-2004 (II). Stratifying for urgency of surgery, but not for tumour site, the 30-day mortality rate was 6.2% after elective surgery and 22.1% after emergency surgery in the period 2001-2008 according to DCCG data (17). Nevertheless, the 30-day mortality was about twice as high in Denmark as in Norway, Sweden and Scotland, even if the data for these countries are older than the Danish data. Mortality rates after palliative surgery are three times higher than the rates following curative surgery (115). The stage distribution at the time of diagnosis is more unfavourable in Denmark than in the other Nordic countries (114). Comparison of survival among countries is, however, encumbered by several methodological issues related to completeness, and data quality of cancer registries, among others, biases the survival estimates.

Like most western populations, the Danish population is ageing and the proportion of elderly colorectal cancer patients aged >75 years has therefore risen from 37% in 1977-1982 to 42% in 1995-1999 (III). Disparity in cancer treatment between elderly and younger patients exists on a number of counts, e.g., the former's curative resection rate is lower, their emergency presentation rate is higher and they are moreover more likely to present with later-stage disease than are younger patients. However, in Denmark the curative resection rate among elderly patients aged >75 years rose from 36% in 1977-1982 to 49% in 1995-1999 (III). This trend was paralleled by an increase in 30-day and 6-month relative survival. Patients aged >70 years have a 30-day mortality rate of 13.1%, but their younger counterparts' mortality rate is only 3.5% (17). A mortality rate at least two to three times higher among the elderly than among younger patients has been reported repeatedly in various populations (95,96,116,127,128,130,131,135,136,144,145).

In Denmark there is an inverse relationship between the comorbidity level and the resection rate in colorectal cancer. In the period 1995-2006, surgical treatment of patients with colonic cancer and severe comorbidity became progressively more aggressive, whereas surgical treatment of patients with rectal cancer apparently became more cautious or differentiated (VI). Nevertheless, the overall 30-day mortality rate after resectional surgery remained stable at about 8% in colonic cancer and at about 6% in rectal cancer. Almost every fourth patient had severe comorbidity as determined by an ASA of III or more and their 30-day mortality rate was at least 18% in 2001-2008. Any reduction in their short-term mortality will therefore have a substantial impact on the overall mortality rate.

Despite the impact of comorbidity on postoperative mortality, the distinct seasonal variation seen in mortality from cardiovascular and respiratory diseases, with excess mortality in the winter months, has not been observed in postoperative mortality from colorectal cancer (VII). Postoperative mortality from colonic cancer was non-significantly higher in July than in other months of the year (VII).

Evidence reveals a volume-outcome relationship regarding postoperative mortality in colonic cancer (IV) and the most recent literature suggests that it probably also is so in rectal cancer. However, volume may be a surrogate marker or proxy for other important structural factors such as quality and capacity of intensive care units, the availability of other clinical services like cardiac care units, multiple medical specialties, multidisciplinary infrastructure and nurse staffing, etc.

Postoperative mortality after emergency surgery for colonic cancer was as high as 22% in 2001-2005 and mortality was significantly associated with the postoperative course. Patients developing medical complications had a mortality rate of 57.8%. Independent risk factors for death within 30 days after surgery were age ≥71 years, male gender, ASA grade ≥ III, palliative outcome, free or iatrogenic tumour perforation, splenectomy, intraoperative surgical adverse events and postoperative medical complications (VIII).

SEMS placement performed on the indication acute bowel obstruction in patients with potentially curable disease can be accomplished with high technical and clinical success rates. The perforation rate, however, may reach 12%. Even so, the mortality rate within 30 days after a SEMS attempt and later surgery may, irrespective of its timing, by very low (3%) relative to the mortality seen after emergency surgery (IX).

### LONG-TERM SURVIVAL

The 5-year relative survival improved by 9% for both colonic and rectal cancer from 1977-1982 to 1995-1999 (I). Further improvement has been observed and in 2004-2006, the 5-year relative survival from colonic cancer was 52% (95% CI 51-54) for men and 57% (95% CI 55-58) for women. For rectal cancer the corresponding percentages were 55% (95% CI 53-57) and 57% (95% CI 55-59) (202). Overall, from 1977 until 2006, 1-year and 5-year survival increased almost 0.5-1% annually. Long-term survival has improved more in rectal cancer than in colonic cancer and survival from rectal cancer surpassed that of colonic cancer in the 2000s (202,204).

Elderly patients aged >75 years experienced a marked 13-16% increase in relative survival from 1977-1982 to 1995-1999, i.e., a period during which the rate of curative surgery increased pronouncedly among the elderly (III). The survival improvement among their younger counterparts in that period only reached 7%. Mortality from colorectal cancer was only excessive in the elderly during the first two years after surgery.

In 1995-2006, about 30-43% of colorectal cancer patients had moderate and severe comorbidity as determined by a Charlson Comorbidity score of 1-2 and 3+, respectively. These comorbid patients had a long-term survival inferior to that of patients with no comorbidity. In colonic cancer, the 5-year survival in 1998-2000 was 43% in patients with no comorbidity and only 20% in patients with severe comorbidity. Comorbidity had an even stronger impact in rectal cancer (VI).

Evidence repeatedly demonstrates a volume-outcome effect on long-term survival from colonic and rectal cancer with improved survival being significantly associated with increasing hospital caseload and surgeon's education/specialty (V). In addition, the

most recent evidence reveals that surgeon caseload may have a stronger impact on long-term survival than hospital volume which reflects the complexity in the interaction between hospital caseload and surgeon caseload.

A total therapeutic delay ≥60 day has been shown to have a negative impact on the long-term survival from rectal cancer, but not from colon cancer, given that stage is an intermediate step in the causal pathway between delay and survival (X). Neither provider delay ≥60 days, nor hospital delays ≥30 days or ≥60 days had any prognostic impact on long-term survival from colorectal cancer. Emergency surgery for colonic cancer is associated with an inferior long-term survival. The 5-year survival after acute curative surgery in Denmark is 39% (16). However, the use of SEMS as bridge to elective curative surgery makes it possible to achieve 3-year survival rates similar to those of 75% seen after elective curative surgery for colonic cancer (IX) – despite an unexpectedly high perforation rate.

## 9. PERSPECTIVES

The best strategy to reduce the colorectal cancer burden is primary prevention, i.e., a lowering of its incidence. The incidence may decline if efforts to change unfavourable life styles characteristic of the Western populations are successful and, probably, if national screening is introduced to reduce the precursor of colorectal cancer: colorectal adenomas. However, an exploration of these aspects is beyond the scope of this thesis, which focussed on different aspects related to mortality and survival from colorectal cancer.

SHORT-TERM OUTCOME
Several factors contribute to the inferior short-term outcome from colorectal cancer in Denmark. Among these factors is the fact that about 18% of Danish patients present with distant metastases and that curative surgery is not achieved in about 22% (17). It would therefore seem reasonable to assume that short-term outcome may improve if (i) patients are diagnosed at earlier stage by implementation of national screening and/or by reducing the therapeutic delay, and (ii) surgeons were better at achieving tumour control, among others by adopting a more aggressive surgical approach, i.e., increase the curative resection rate.

Other factors contributing to the inferior short-term outcome include, e.g., advanced age, comorbidity and emergency presentation – all of which are discussed below.

Elderly patients' short-term mortality is two to three times higher than that of their younger counterparts. Their increased level of comorbidity and decreased physiological reserve contribute to this situation. Currently, major progress within the area of minimally invasive surgical techniques like laparoscopic surgery continues, which will probably further improve the short-time outcome (262,263).

Surgical decision-making about elderly colorectal cancer patients continues to be a major challenge. A curative resection rate of around 50% among the elderly in the late 1990s and at the same time an excess mortality within 6 months of surgery are indicators of less than optimal surgical decision-making and peri-operative care of the elderly. It has been suggested that the elderly should undergo a preoperative comprehensive geriatric assessment in order to assess frailty (123). It has even been stated that presenting data on elderly patients without frailty information is as unacceptable as presenting cancer data without stage information (264). The main drawback of the comprehensive geriatric assessment, however, is that it is time-consuming. The question is therefore whether elderly should be evaluated and treated by multidisciplinary teams including also geriatric specialists. Clinicians have to decide among a growing number of beneficial (palliative) treatment regimens and they have to individualize treatment of the elderly even more than treatment of their younger counterparts and surgery is scarcely the best option in everyone. Patients of the same age may be fit, have no comorbidity and have a high physical activity level or they may be frail and have severe comorbidity and functional impairment (265). Some elderly may certainly be too frail to withstand a postoperative course and such patients may best be managed by supportive or palliative care. However, even some frail, high-risk patients do need surgery because of severe tumour-related symptoms - and among these some will inevitably die in the postoperative course.

Several questions regarding the elderly remain unanswered: Why do elderly more frequently present as emergencies? Do elderly ignore symptoms suggestive of colorectal cancer more frequently than their younger counterparts? Are the caregivers less aware of colorectal cancer among elderly? Have the caregivers abstained from offering elderly patients surgery? Or do the elderly patients themselves decline the offer of surgery? Treatment of the elderly and an improvement in their outcome may be accomplished if these questions can be answered by future research.

Most of the considerations regarding the elderly can be applied to the comorbid patients as well. Comorbidity, age and frailty are interrelated. Interestingly, the resection rate has increased among comorbid colonic cancer patients and at the same time the mortality rate has remained stable.

Unexpectedly, a non-significant increase in postoperative mortality from colonic cancer was observed for July – and it was most pronounced in patients with comorbidity. This July effect should be elucidated further and its association with the staffing level at hospitals during summer vacation should be examined.

The main contributors to postoperative mortality after emergency surgery for colonic cancer are elderly patients, comorbid patients and patients who develop medical complications. Efforts should therefore be directed towards prevention and/or early recognition of medical complications which should be combined with appropriate treatment. Such an approach is expected to substantially reduce the 30-day mortality after emergency. Furthermore, the emergency rate must be reduced, which can be done by implementation of national screening as has been observed in England (Phil Quirke, unpublished data).

The use of SEMS in patients with obstruction is another option that may reduce the emergency rate. Many clinicians are reluctant to embrace this approach, partly because of its adverse events like perforation. There is no doubt that the perforation rate requires further attention as perforation is the main mortality factor (188). In addition, in patients with non-acute incurable obstruction, the long-term outcome of SEMS should be further studied due to the late complications like perforation, migration, re-obstruction caused by tumour in-growth or overgrowth and faecal impaction in patients on palliative chemotherapy.

The benefit of high volume and specialization on postoperative mortality seems evident even if the literature has identified several limitations. A further centralization and specialization therefore seems to be warranted, at least from the author's common sense point of view, in order to reduce the persistent, high postoperative mortality rate in Denmark. Even a small-scale benefit achieved by such centralization may have much impact; not least

if the burden-incidence of colorectal cancer with the ageing, comorbid, high-risk patients is taken into consideration. The fact that the Danish nationwide studies examining the volume-outcome effect have examined the effect mainly among low-volume hospitals underscores the importance of the need for further studies using cut-points based on graded volumes and studying the effect among high-volume hospitals in detail. There is also a need for studies adjusted for, e.g., the quality of surgery. Better understanding of surgical risk is crucial to treatment optimization. In case patients at high risk of postoperative death can be identified preoperatively, the clinicians will probably be able to better tailor management to the patient's needs and to recognize and treat any complication timely, although evidence for the latter is missing. Several risk scoring systems have been designed to predict the risk of death. None of them have been evaluated in Danish colorectal cancer patients and Denmark has not yet focussed much on the country's high level of postoperative mortality. The author and her collaborators plan to develop a Danish risk-scoring system and to evaluate the effect of more individualized management. While awaiting the development of such risk scoring systems or easy-to-use comprehensive geriatric assessment tools, management of colorectal cancer patients should be tailored to comorbidity rather than age per se (125).

As a result of advances in medical treatment and supportive care at intensive care units, several postoperative complications are now being treated more efficiently although some of the patients may ultimately die after the immediate postoperative period. Especially elderly and comorbid patients may die following a stay at an intensive care unit extending 30 days after surgery. Therefore, short-term mortality should not be evaluated by the 30-day mortality rate only; assessment of the mortality rate after 90 days or 180 days would be more appropriate.

LONG-TERM OUTCOME

The high level of short-term mortality inevitably implies that also long-term survival from colorectal cancer is inferior in Denmark. However, long-term survival from rectal cancer has improved after the implementation of TME surgery, the introduction of preoperative radiotherapy, the concentration of surgery at fewer hospitals and the establishment of MDTs. We may reasonably expect a similar improvement in the long-term outcome from colonic cancer if such optimization and focus on treatment could be accomplished. Hohenberger has achieved a favourable outcome of the CME technique in colonic cancer. The future will show whether these favourable results are reproducible. Furthermore, we must ask ourselves whether this technique can be learned/implemented by all surgeons, if it should be used in all cases or if it must be modified. A more detailed preoperative evaluation of the T-stage of colonic cancer would probably aid selection of patients to different operative regimens like laparoscopic technique, conventional surgery and CME, etc. The Danish guidelines on colonic resection are defined by the vascular ligation and hence the adequacy of vascular supply to the intended anastomotic segments. However, a recent Swedish study has suggested that the high logo-regional recurrence rate of sigmoid cancer was caused by surgeons performing minor wedge-like resections (266). Thus, focus should be on making true central vascular ligation and adequate bowel resection margins in colonic surgery with a curative intent. The results of the randomized trial FOxTROT (267) will also answer the question whether neo-adjuvant chemotherapy in locally advanced colonic tumours has any effect on long-term survival.

The survival improvement in elderly that accompanied the growing use of curative resection should also be emphasized. Surgical resection is the optimal treatment for colorectal cancer and should be offered to fit elderly independently of their chronological age. It is important to remember the fact that a person who has reached the age of 80 years will have a relatively longer life expectancy than younger persons. Also, importantly, if an elderly is offered surgery, it should be with a curative intent. In the future, the benefit of preoperative radiotherapy in elderly rectal cancer patients must be elucidated.

Comorbidity adversely affects long-term survival. It remains unresolved whether the present treatment of comorbidities is appropriate and efforts should be directed against evaluation of the appropriateness of comorbidity treatment in the pre-, intra-, and postoperative period. Optimization of surgical decision-making in comorbid patients is yet another target for future research.

Evidence demonstrates that survival from colorectal cancer depends more or less on the hospital caseload, surgeon caseload and surgeon specialty. Given that four Danish surgical departments treated less than 50 colonic cancer patients per year in 2008 and eight departments treated less than 75 patients (17), the Danish hospital structure for surgical management of colorectal cancer has seemingly not yet been organized in a manner that allows it to achieve an optimal outcome. The Danish hospital structure should therefore undergo further centralization and specialization. Moreover, MDTs should be established covering all specialties relevant to the management of colorectal cancer in each unit to minimize the detrimental volume-specialty-outcome effect on colorectal cancer survival. Importantly, by increasing the hospital volume, treatment feedback and benchmarking would be more powerful and thus more real and meaningful and a Hawthorne effect may probably be observed, i.e., underperforming departments will make every possible effort to improve their quality.

Both patient delay and hospital delay are rather long and the fact that a total therapeutic delay ≥60 day has a negative impact on long-term survival among rectal cancer patients calls for a reduction of delay. Patients should therefore be educated to become aware of their symptoms and, probably more importantly, to understand how and when to act on these symptoms (239,268). Hospital delay may hopefully decrease because of the introduction of fast-track referral for diagnosis and treatment in late 2000s and because of the third National Cancer Plan's recommendation of fast-track pathways also for patients with potential cancer symptoms that do not fulfil the urgent referral criteria.

Stent-related tumour perforations observed in 4-12% of emergency-stented patients is a matter of great concern both in patients having SEMS as bridge to elective surgery and in patients having SEMS as a definitive palliative procedure. In the former, the optimal time period from SEMS placement to elective surgery has to be defined. In the future, long-term results of two ongoing randomized trials comparing SEMS insertions with emergency surgery may determine the most optimal treatment method in acute bowel obstruction. Meanwhile, SEMS insertion may be recommended in patients not suspected of having concomitant perforation.

To monitor colorectal cancer outcome properly and to get robust evidence timely of any advances or disadvantages of new treatment regimens, national cancer registration should continue to be developed ensuring complete ascertainment and correct data collection. This will allow the production of up-to-date survival estimates, feedback and benchmarking.

## 12. REFERENCES

1. Sant M, Capocaccia R, Verdecchia A et al.: Comparisons of colon-cancer survival among European countries: The Eurocare Study. Int J Cancer 1995: 63:43-48.
2. Gatta G, Capocaccia R, Sant M et al.: Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high resolution study. Gut 2000: 47:533-538.
3. Gatta G, Capocaccia R, Coleman MP et al.: Toward a comparison of survival in American and European cancer patients. Cancer 2000: 89:893-900.
4. Sackett D, Haynes R, Guyatt G, Tugwell P: "Clinical epidemiology. A basic science for clinical medicine." Boston/Toronto/London: Library of Congress Card, 1991.
5. Hole DJ, McArdle CS: Impact of socioeconomic deprivation on outcome after surgery for colorectal cancer. Br J Surg 2002: 89:586-590.
6. Coleman MP, Rachet B, Woods LM et al.: Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. Br J Cancer 2004: 90:1367-1373.
7. Engeland A, Haldorsen T, Dickman PW et al.: Relative survival of cancer patients--a comparison between Denmark and the other Nordic countries. Acta Oncol 1998: 37:49-59.
8. National kræftplan. 2000. Sundhedsstyrelsen. http://www.sst.dk/publ/Publ2000/Kraeft/National_kraeftplan_1.pdf
9. Sant M, Capocaccia R, Coleman MP et al.: Cancer survival increases in Europe, but international differences remain wide. Eur J Cancer 2001: 37:1659-1667.
10. Harling H, Bulow S, Kronborg O et al.: Survival of rectal cancer patients in Denmark during 1994-99. Colorectal Dis 2004: 6:153-157.
11. Cancerregisteret 2000. Sundhedsstyrelsen. 2004. http://www.sst.dk/publ/tidsskrifter/nyetal/pdf/2004/17_04.pdf
12. Cancerregisteret 2009. Sundhedsstyrelsen. 2010. http://www.sst.dk/publ/Publ2010/DOKU/Registre/Cancerregisteret2009.pdf
13. Kræftplan II. 2005. Sundhedsstyrelsen. http://www.sst.dk/publ/publ2005/plan/kraeftplan2/Kraeftepidemiologi_rapport.pdf
14. Sundhedsstyrelsen 2009. Sygehusbaseret overlevelse for udvalgte kræftsygdomme 1994-2005. www.sst.dk/publ/tidsskrifter/nyetal/pdf/2006/08_06.pdf
15. Korsgaard M, Pedersen L, Sorensen HT, Laurberg S: Reported symptoms, diagnostic delay and stage of colorectal cancer: a population-based study in Denmark. Colorectal Dis 2006: 8:688-695.
16. Danish Colorectal Cancer Group. Annual review 2006. Nationwide database on colonic and rectal cancer (in Danish). http://www.dccg.dk/03_Publikation/02_arsraport_pdf/aasrapport_2006.pdf
17. Danish Colorectal Cancer Group. Annual review 2007-2008. Nationwide database on colonic and rectal in Denmark, revised version (in Danish). http://www.dccg.dk/03_Publikation/02_arsraport_pdf/revideret_aarsrapport_2007_2009.pdf
18. Dukes CE: The classification of the rectum. J Pathol Bacteriol 1932: 35:323-332.
19. Wittekind C, Green FL, Hutter RVP et al.: "TNM Atlas: Illustrated guide to the TNM classification of malignant tumours." Springer Verlag, 2006.
20. Moran B, Brown G, Cunningham D et al.: Clarifying the TNM staging of rectal cancer in the context of modern imaging and neo-adjuvant treatment: 'y''u' and 'p' need 'mr' and 'ct'. Colorectal Dis 2008: 10:242-243.
21. Danish Colorectal Cancer Group. Annual review 2004. Nationwide database on colonic and rectal cancer (in Danish). http://www.dccg.dk/03_Publikation/02_arsraport_pdf/KRC_aarsrapport2004.pdf
22. Feinstein AR, Sosin DM, Wells CK: The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med 1985: 312:1604-1608.
23. Danish Society of Surgery. Guidelines for the diagnosis and the management of colorectal cancer (in Danish). 1998.
24. Danish Society of Surgery. Guidelines for the diagnosis and the management of colorectal cancer (in Danish). 2. edition, 2002. http://www.jimlarsen.dk/Arkiv/Artikler_onk/DCCG2002.pdf
25. Danish Society of Surgery and Danish Colorectal Cancer Group. Guidelines for the diagnosis and the management of colorectal cancer (in Danish). 3. edition, 2005. http://www.kirurgisk-selskab.dk/dks/guidelines/krc/trykklar%20Bog8.pdf
26. Danish Colorectal Cancer Group. Guidelines for the diagnosis and the management of colorectal cancer (in Danish). DCCG (4. edition, 2009, revised October 2010). http://www.dccg.dk/03_Publikation/Retningslinier2009revOKT2010.pdf
27. Kronborg O, Fenger C, Olsen J et al.: Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996: 348:1467-1471.
28. Sundhedsstyrelsen. Screening for tarmkræft deltagelsesprocentens betydning – En medicinsk teknologivurdering. 2008. http://www.sst.dk/publ/Publ2008/MTV/screening_tarmkraeft/MTV_tarmkraeft_net_final_version2.pdf
29. Statens Institut for Medicinsk Teknologivurdering. Kræft i tyktarm og endetarm, Diagnostik og screening (in Danish). 2001. http://www.cemtv.dk/publikationer/docs/kolorektal/marts2001/pdf/Kolorektal1-38.pdf
30. Bjerregaard NC, Tottrup A, Sorensen HT, Laurberg S: Evaluation of the Danish national strategy for selective use of colonoscopy in symptomatic outpatients without known risk factors for colorectal cancer. Scand J Gastroenterol 2007: 42:228-236.
31. Sundhedsstyrelsen. Sundhedsøkonomisk analyse af diagnostiske strategier ved symptomer på ende- og tyktarmskræft - en medicinsk teknologivurdering. 2009. http://www.sst.dk/publ/publ2009/MTV/tarmkraeft/MTV_tarmkraeft_net_final.pdf
32. Olesen F, Hansen RP, Vedsted P: Delay in diagnosis: the experience in Denmark. Br J Cancer 2009: 101 Suppl 2:S5-S8.
33. Basse L, Thorbol JE, Lossl K, Kehlet H: Colonic surgery with accelerated rehabilitation or conventional care. Dis Colon Rectum 2004: 47:271-277.

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

35. Zirngibl H, Husemann B, Hermanek P: Intraoperative spillage of tumor cells in surgery for rectal cancer. Dis Colon Rectum 1990: 33:610-614.

36. Schwenk W, Haase O, Neudecker J, Muller JM: Short term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev 2005:CD003145.

37. Kuhry E, Schwenk WF, Gaupset R et al.: Long-term results of laparoscopic colorectal cancer resection. Cochrane Database Syst Rev 2008:CD003432.

38. Hohenberger W, Weber K, Matzel K et al.: Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. Colorectal Dis 2009: 11:354-364.

39. De Salvo GL, Gava C, Pucciarelli S, Lise M: Curative surgery for obstruction from primary left colorectal carcinoma: primary or staged resection? Cochrane Database Syst Rev 2004:CD002101.

40. Tejero E, Mainar A, Fernandez L et al.: New procedure for the treatment of colorectal neoplastic obstructions. Dis Colon Rectum 1994: 37:1158-1159.

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

42. Holm T, Ljung A, Haggmark T et al.: Extended abdominoperineal resection with gluteus maximus flap reconstruction of the pelvic floor for rectal cancer. Br J Surg 2007: 94:232-238.

43. Christensen H, Nerstrøm P, Tei T, Laurberg S: Perineal repair after extralevatory abdominoperineal excision for low rectal cancer. Dis Colon Rectum 2011: 54:711-717.

44. Balslev I, Pedersen M, Teglbjaerg PS et al.: Postoperative radiotherapy in Dukes' B and C carcinoma of the rectum and rectosigmoid. A randomized multicenter study. Cancer 1986: 58:22-28.

45. Lundby L, Jensen VJ, Overgaard J, Laurberg S: Long-term colorectal function after postoperative radiotherapy for colorectal cancer. Lancet 1997: 350:564.

46. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997: 336:980-987.

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

48. Kapiteijn E, Marijnen CAM, Nagtegaal ID et al.: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001: 345:638-46.

49. Peeters KC, van de Velde CJ, Leer JW et al.: Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. J Clin Oncol 2005: 23:6199-6206.

50. Gerard JP, Conroy T, Bonnetain F et al.: Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006: 24:4620-4625.

51. Moertel CG, Fleming TR, Macdonald JS et al.: Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990: 322:352-358.

52. Glimelius B, Cedermark B, Dahl O et al. Adjuvant chemotheraphy in colorectal cancer: Joint analyses of randomised trials by the Nordic Gastrointestinal Tumour Adjuvant Theraphy Group. Eur.J.Cancer Supplements 1[5], S318. 2003.

53. Iversen LH, Rasmussen PC, Laurberg S: New treatment of peritoneal carcinomatosis from colorectal cancer. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ugeskr Laeger 2007: 169:3179-3181.

54. Dohmoto M: New Method: endoscopic implantation of rectal stent in palliative treatment of malignant stenosis. Endoscopia Digestiva 1991: 3:1507-1512.

55. Scheithauer W, Rosen H, Kornek GV et al.: Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. BMJ 1993: 306:752-755.

56. Simmonds PC: Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. BMJ 2000: 321:531-535.

57. Pedersen KM, Christiansen T, Bech M: The Danish health care system: evolution--not revolution - in a decentralized system. Health Econ 2005: 14:S41-S57.

58. Danish Colorectal Cancer Group. Annual review 2005. Nationwide database on colonic and rectal cancer (in Danish).
http://www.dccg.dk/03_Publikation/02_arsraport_pdf/KRC_aarsrapport2005.pdf

59. Frank L: When an entire country is a cohort. Science 2000: 287:2398-2399.

60. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB: The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull 2006: 53:441-449.

61. Carstensen B: Survival of Danish cancer patients 1943-1987. Material and methods. APMIS Suppl 1993: 33:3-8.:3-8.

62. Storm HH, Michelsen EV, Clemmensen IH, Pihl J: The Danish Cancer Registry - history, content, quality and use. Dan Med Bull 1997: 44:535-539.

63. Andersen TF, Madsen M, Jørgensen J et al.: The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999: 46:263-268.

64. NOMESCO Classification of Surgical Procedures. 2007. www.nordclass.uu.se/

65. Nickelsen TN: Data validity and coverage in the Danish National Health Registry. A literature review. Ugeskr Laeger 2001: 164:33-37.

66. Mosbech J, Jorgensen J, Madsen M et al.: The national patient registry. Evaluation of data quality. Ugeskr Laeger 1995: 157:3741-3745.

67. Norgaard M, Larsson H, Pedersen G et al.: Haematological malignancies--a predictor of a poor outcome in patients with bacteraemia. J Infect 2006: 53:190-198.

68. Tetsche MS, Norgaard M, Skriver MV et al.: Accuracy of ovarian cancer ICD-10 diagnosis in a Danish population-based hospital discharge registry. Eur J Gynaecol Oncol 2005: 26:266-270.

69. Nickelsen TN, Harling H, Kronborg O et al.: The completeness and quality of the Danish Colorectal Cancer clinical database on colorectal cancer. Ugeskr Laeger 2004: 166:3092-3095.

70. de Vries E, Karim-Kos HE, Janssen-Heijnen ML et al.: Explanations for worsening cancer survival. Nat Rev Clin Oncol 2010: 7:60-63.
71. Danmarks Statistik. 2011.http://www.statistikbanken.dk/statbank5a/default.asp?w=1280
72. Extermann M: Interaction between comorbidity and cancer. Cancer Control 2007: 14:13-22.
73. Prior P, Woodman CB, Collins S: International differences in survival from colon cancer: more effective care versus less complete cancer registration. Br J Surg 1998: 85:101-104.
74. Robinson D, Sankila R, Hakulinen T, Moller H: Interpreting international comparisons of cancer survival: the effects of incomplete registration and the presence of death certificate only cases on survival estimates. Eur J Cancer 2007: 43:909-913.
75. Beral V, Peto R: UK cancer survival statistics. BMJ 2010: 341:c4112. doi: 10.1136/bmj.c4112.:c4112.
76. World Populations Prospects. The 2006 revision. http://www.un.org/esa/population/publications/wpp2006/WPP2006_Highlights_rev.pdf
77. Engholm G, Kejs AM, Brewster DH et al.: Colorectal cancer survival in the Nordic countries and the United Kingdom: excess mortality risk analysis of 5 year relative period survival in the period 1999 to 2000. Int J Cancer 2007: 121:1115-1122.
78. Platell CF, Semmens JB: Review of survival curves for colorectal cancer. Dis Colon Rectum 2004: 47:2070-2075.
79. Association of the Nordic Cancer Registries. 2011. http://www.ancr.nu/default_old.asp
80. Autier P, Boniol M: Caution needed for country-specific cancer survival. Lancet 2011: 377:99-101.
81. Autier P, Boniol M, Hery C et al.: Cancer survival statistics should be viewed with caution. Lancet Oncol 2007: 8:1050-1052.
82. Jemal A, Siegel R, Xu J, Ward E: Cancer statistics, 2010. CA Cancer J Clin 2010: 60:277-300.
83. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987: 40:373-383.
84. Dripps R: New classification of physical status. Anesthesiology 1963: 24:111.
85. Extermann M: Measurement and impact of comorbidity in older cancer patients. Crit Rev Oncol Hematol 2000: 35:181-200.
86. Newschaffer CJ, Bush TL, Penberthy LT: Comorbidity measurement in elderly female breast cancer patients with administrative and medical records data. J Clin Epidemiol 1997: 50:725-733.
87. Singh B, Bhaya M, Stern J et al.: Validation of the Charlson comorbidity index in patients with head and neck cancer: a multi-institutional study. Laryngoscope 1997: 107:1469-1475.
88. Zingmond D, Maggard M, O'Connell J et al.: What predicts serious complications in colorectal cancer resection? Am Surg 2003: 69:969-974.
89. Tetsche MS, Norgaard M, Jacobsen J et al.: Comorbidity and ovarian cancer survival in Denmark, 1995-2005: a population-based cohort study. Int J Gynecol Cancer 2007: 18: 421-427.
90. Jeldres C, Suardi N, Walz J et al.: Poor Overall Survival in Septa- and Octogenarian Patients after Radical Prostatectomy and Radiotherapy for Prostate Cancer: A Population-Based Study of 6183 Men. Eur Urol 2007: 54: 107-116.
91. Alibhai SM, Leach M, Tomlinson GA et al.: Is there an optimal comorbidity index for prostate cancer? Cancer 2008: 112:1043-1050.
92. Extermann M, Overcash J, Lyman GH et al.: Comorbidity and functional status are independent in older cancer patients. J Clin Oncol 1998: 16:1582-1587.
93. Baldwin LM, Klabunde CN, Green P et al.: In search of the perfect comorbidity measure for use with administrative claims data: does it exist? Med Care 2006: 44:745-753.
94. Hines RB, Chatla C, Bumpers HL et al.: Predictive capacity of three comorbidity indices in estimating mortality after surgery for colon cancer. J Clin Oncol 2009: 27:4339-4345.
95. Engel AF, Oomen JL, Knol DL, Cuesta MA: Operative mortality after colorectal resection in the Netherlands. Br J Surg 2005: 92:1526-1532.
96. Endreseth BH, Romundstad P, Myrvold HE et al.: Rectal cancer treatment of the elderly. Colorectal Dis 2006: 8:471-479.
97. Sjovall A, Holm T, Singnomklao T et al.: Colon cancer management and outcome in relation to individual hospitals in a defined population. Br J Surg 2007: 94:491-499.
98. Sjo OH, Larsen S, Lunde OC, Nesbakken A: Short term outcome after emergency and elective surgery for colon cancer. Colorectal Dis 2009: 11:733-739.
99. Borowski DW, Bradburn DM, Mills SJ et al.: Volume-outcome analysis of colorectal cancer-related outcomes. Br J Surg 2010: 97:1416-1430.
100. Longo WE, Virgo KS, Johnson FE et al.: Risk factors for morbidity and mortality after colectomy for colon cancer. Dis Colon Rectum 2000: 43:83-91.
101. Fazio VW, Tekkis PP, Remzi F, Lavery IC: Assessment of operative risk in colorectal cancer surgery: the Cleveland Clinic Foundation colorectal cancer model. Dis Colon Rectum 2004: 47:2015-2024.
102. Slim K, Panis Y, Alves A et al.: Predicting postoperative mortality in patients undergoing colorectal surgery. World J Surg 2006: 30:100-106.
103. Davila JA, Rabeneck L, Berger DH, El Serag HB: Postoperative 30-day mortality following surgical resection for colorectal cancer in veterans: changes in the right direction. Dig Dis Sci 2005: 50:1722-1728.
104. Marusch F, Koch A, Schmidt U et al.: The impact of the risk factor "age" on the early postoperative results of surgery for colorectal carcinoma and its significance for perioperative management. World J Surg 2005: 29:1013-1021.
105. Khuri SF, Henderson WG, DePalma RG et al.: Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005: 242:326-341.
106. Matthiessen P, Hallbook O, Rutegard J, Sjodahl R: Population-based study of risk factors for postoperative death after anterior resection of the rectum. Br J Surg 2006: 93:498-503.

107. Tekkis PP, Prytherch DR, Kocher HM et al.: Development of a dedicated risk-adjustment scoring system for colorectal surgery (colorectal POSSUM). Br J Surg 2004: 91:1174-1182.

108. Tekkis PP, Poloniecki JD, Thompson MR, Stamatakis JD: Operative mortality in colorectal cancer: prospective national study. BMJ 2003: 327:1196-1201.

109. Heriot AG, Tekkis PP, Smith JJ et al.: Prediction of post-operative mortality in elderly patients with colorectal cancer. Dis Colon Rectum 2006: 49:816-824.

110. Bulow S, Harling H, Iversen LH, Ladelund S: Improved survival after rectal cancer in Denmark. Colorectal Dis 2009: 12 (7 Online): e37-42.

111. McArdle CS, Hole DJ: Emergency presentation of colorectal cancer is associated with poor 5-year survival. Br J Surg 2004: 91:605-609.

112. Storm HH, Dickman PW, Engeland A et al.: Do morphology and stage explain the inferior lung cancer survival in Denmark? Eur Respir J 1999: 13:430-435.

113. Jensen AR, Garne JP, Storm HH et al.: Does stage at diagnosis explain the difference in survival after breast cancer in Denmark and Sweden? Acta Oncol 2004: 43:719-726.

114. Folkesson J, Engholm G, Ehrnrooth E et al.: Rectal cancer survival in the Nordic countries and Scotland. Int J Cancer 2009: 125:2406-2412.

115. Nickelsen TN, Jorgensen T, Kronborg O: Thirty-day mortality after surgery for colorectal cancer in Denmark. Colorectal Dis 2005: 7:500-506.

116. Mitry E, Bouvier AM, Esteve J, Faivre J: Benefit of operative mortality reduction on colorectal cancer survival. Br J Surg 2002: 89:1557-1562.

117. Vercelli M, Quaglia A, Casella C et al.: Relative survival in elderly cancer patients in Europe. Eur J Cancer 1998: 34:2264-2270.

118. Vercelli M, Capocaccia R, Quaglia A et al.: Relative survival in elderly European cancer patients: evidence for health care inequalities. The EUROCARE Working Group. Crit Rev Oncol Hematol 2000: 35:161-179.

119. Agarwal N, Leighton L, Mandile MA, Cayten CG: Outcomes of surgery for colorectal cancer in patients age 80 years and older. Am J Gastroenterol 1990: 85:1096-1101.

120. Edna TH, Bjerkeset T: Colorectal cancer in patients over 80 years of age. Hepatogastroenterology 1998: 45:2142-2145.

121. Yancik R, Wesley MN, Ries LA et al.: Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients: a population-based study. Cancer 1998: 82:2123-2134.

122. Martin FC, Brighton P: Frailty: different tools for different purposes? Age Ageing 2008: 37:129-131.

123. Kristjansson SR, Nesbakken A, Jordhoy MS et al.: Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: a prospective observational cohort study. Crit Rev Oncol Hematol 2010: 76:208-217.

124. Kristjansson SR, Farinella E, Gaskell S, Audisio RA: Surgical risk and post-operative complications in older unfit cancer patients. Cancer Treat Rev 2009: 35:499-502.

125. Audisio RA, Pope D, Ramesh HS et al.: Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. Crit Rev Oncol Hematol 2008: 65:156-163.

126. Gatta G, Sant M, Coebergh JW, Hakulinen T: Substantial variation in therapy for colorectal cancer across Europe: EUROCARE analysis of cancer registry data for 1987. Eur J Cancer 1996: 32A:831-835.

127. Violi V, Pietra N, Grattarola M et al.: Curative surgery for colorectal cancer: long-term results and life expectancy in the elderly. Dis Colon Rectum 1998: 41:291-298.

128. Marusch F, Koch A, Schmidt U et al.: Impact of age on the short-term postoperative outcome of patients undergoing surgery for colorectal carcinoma. Int J Colorectal Dis 2002: 17:177-184.

129. Townsley C, Pond GR, Peloza B et al.: Analysis of treatment practices for elderly cancer patients in Ontario, Canada. J Clin Oncol 2005: 23:3802-3810.

130. Latkauskas T, Rudinskaite G, Kurtinaitis J et al.: The impact of age on post-operative outcomes of colorectal cancer patients undergoing surgical treatment. BMC Cancer 2005: 5:153.

131. Tan E, Tilney H, Thompson M et al.: The United Kingdom National Bowel Cancer Project -- epidemiology and surgical risk in the elderly. Eur J Cancer 2007: 43:2285-2294.

132. van Leeuwen BL, Pahlman L, Gunnarsson U et al.: The effect of age and gender on outcome after treatment for colon carcinoma. A population-based study in the Uppsala and Stockholm region. Crit Rev Oncol Hematol 2008: 67:229-236.

133. Jung B, Pahlman L, Johansson R, Nilsson E: Rectal cancer treatment and outcome in the elderly: an audit based on the Swedish Rectal Cancer Registry 1995-2004. BMC Cancer 2009: 9:68.

134. Lemmens V, van Steenbergen L, Janssen-Heijnen M et al.: Trends in colorectal cancer in the south of the Netherlands 1975-2007: rectal cancer survival levels with colon cancer survival. Acta Oncol 2010: 49:784-796.

135. Elferink MA, Wouters MW, Krijnen P et al.: Disparities in quality of care for colon cancer between hospitals in the Netherlands. Eur J Surg Oncol 2010: 36 Suppl 1:S64-S73.

136. Elferink MA, Krijnen P, Wouters MW et al.: Variation in treatment and outcome of patients with rectal cancer by region, hospital type and volume in the Netherlands. Eur J Surg Oncol 2010: 36 Suppl 1:S74-S82.

137. Mitry E, Bouvier AM, Esteve J, Faivre J: Improvement in colorectal cancer survival: a population-based study. Eur J Cancer 2005: 41:2297-2303.

138. Surgery for colorectal cancer in elderly patients: a systematic review. Colorectal Cancer Collaborative Group. Lancet 2000: 356:968-974.

139. Arveux I, Boutron MC, El Mrini T et al.: Colon cancer in the elderly: evidence for major improvements in health care and survival. Br J Cancer 1997: 76:963-967.

140. Rutten H, den Dulk M, Lemmens V et al.: Survival of elderly rectal cancer patients not improved: analysis of population based data on the impact of TME surgery. Eur J Cancer 2007: 43:2295-2300.

141. Faiz O, Haji A, Bottle A et al.: Elective colonic surgery for cancer in the elderly: an investigation into postoperative mortality in English NHS hospitals between 1996 and 2007. Colorectal Dis 2011: 13:779-785.

142. Rutten HJ, den Dulk M, Lemmens VE et al.: Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol 2008: 9:494-501.

143. Visser BC, Keegan H, Martin M, Wren SM: Death after colectomy: it's later than we think. Arch Surg 2009: 144:1021-1027.

144. Damhuis RA, Wereldsma JC, Wiggers T: The influence of age on resection rates and postoperative mortality in 6457 patients with colorectal cancer. Int J Colorectal Dis 1996: 11:45-48.

145. Faivre J, Lemmens VE, Quipourt V, Bouvier AM: Management and survival of colorectal cancer in the elderly in population-based studies. Eur J Cancer 2007: 43:2279-2284.

146. Puig-La Calle J, Jr., Quayle J, Thaler HT et al.: Favorable short-term and long-term outcome after elective radical rectal cancer resection in patients 75 years of age or older. Dis Colon Rectum 2000: 43:1704-1709.

147. De Marco MF, Janssen-Heijnen ML, van der Heijden LH, Coebergh JW: Comorbidity and colorectal cancer according to subsite and stage: a population-based study. Eur J Cancer 2000: 36:95-99.

148. Lemmens VE, Janssen-Heijnen ML, Verheij CD et al.: Comorbidity leads to altered treatment and worse survival of elderly patients with colorectal cancer. Br J Surg 2005: 92:615-623.

149. Janssen-Heijnen ML, Maas HAAM, Houterman S et al.: Comorbidity in older surgical cancer patients: Influence on patient care and outcome. Eur J Cancer 2007: 43:2179-2193.

150. Sarfati D, Hill S, Blakely T et al.: The effect of comorbidity on the use of adjuvant chemotherapy and survival from colon cancer: a retrospective cohort study. BMC Cancer 2009: 9: 116.

151. The Association of Coloproctology of Great Britain and Ireland. Report of the The National Bowel Cancer Audit Project "Assessing Quality" June 2006. http://www.nbocap.org.uk/resources/reports/ACP_report_2006.pdf

152. Nationellt kvalitetsregister Cancer rekti (Swedish). Onkologiskt centrum, Norrlands universitetssjukhus, 901 85 Umeå . 2009. http://www.ocsyd.se/VP-verksamhet/Kvalitetsreg/Statistik_CaRecti2009_100624.pdf

153. Frederiksen BL, Osler M, Harling H et al.: The impact of socioeconomic factors on 30-day mortality following elective colorectal cancer surgery: a nationwide study. Eur J Cancer 2009: 45:1248-1256.

154. Vilkman S, Keistinen T, Tuuponen T, Kivela SL: Seasonal variation in hospital admissions for chronic obstructive pulmonary disease in Finland. Arctic Med Res 1996: 55:182-186.

155. Stewart S, McIntyre K, Capewell S, McMurray JJ: Heart failure in a cold climate. Seasonal variation in heart failure-related morbidity and mortality. J Am Coll Cardiol 2002: 39:760-766.

156. Frost L, Johnsen SP, Pedersen L et al.: Seasonal variation in hospital discharge diagnosis of atrial fibrillation: a population-based study. Epidemiology 2002: 13:211-215.

157. Murphy NF, Stewart S, MacIntyre K et al.: Seasonal variation in morbidity and mortality related to atrial fibrillation. Int J Cardiol 2004: 97:283-288.

158. Carder M, McNamee R, Beverland I et al.: The lagged effect of cold temperature and wind chill on cardiorespiratory mortality in Scotland. Occup Environ Med 2005: 62:702-710.

159. Fleming DM: The contribution of influenza to combined acute respiratory infections, hospital admissions, and deaths in winter. Commun Dis Public Health 2000: 3:32-38.

160. Florez-Duquet M, McDonald RB: Cold-induced thermoregulation and biological aging. Physiol Rev 1998: 78:339-358.

161. Gunnarsson H, Holm T, Ekholm A, Olsson L: Emergency presentation of colon cancer is most frequent during summer. Colorectal Dis 2011: 13:663-668.

162. Roychoudhuri R, Robinson D, Coupland V et al.: Season of cancer diagnosis exerts distinct effects upon short- and long-term survival. Int J Cancer 2009: 124:2436-2441.

163. Luft HS, Bunker JP, Enthoven AC: Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med 1979: 301:1364-1369.

164. Begg CB, Cramer LD, Hoskins WJ, Brennan MF: Impact of hospital volume on operative mortality for major cancer surgery. JAMA 1998: 280:1747-1751.

165. Halm EA, Lee C, Chassin MR: Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Ann Intern Med 2002: 137:511-520.

166. Salz T, Sandler RS: The effect of hospital and surgeon volume on outcomes for rectal cancer surgery. Clin Gastroenterol Hepatol 2008: 6:1185-1193.

167. Gruen RL, Pitt V, Green S et al.: The effect of provider case volume on cancer mortality: systematic review and meta-analysis. CA Cancer J Clin 2009: 59:192-211.

168. van Gijn W, Gooiker GA, Wouters MW et al.: Volume and outcome in colorectal cancer surgery. Eur J Surg Oncol 2010: 36 Suppl 1:S55-S63.

169. Archampong D, Borowski DW, Dickinson HO: Impact of surgeon volume on outcomes of rectal cancer surgery: a systematic review and meta-analysis. Surgeon 2010: 8:341-352.

170. Nugent E, Neary P: Rectal cancer surgery: volume-outcome analysis. Int J Colorectal Dis 2010: 25:1389-1396.

171. Ho V, Heslin MJ, Yun H, Howard L: Trends in hospital and surgeon volume and operative mortality for cancer surgery. Ann Surg Oncol 2006: 13:851-858.

172. Rogers SO, Jr., Wolf RE, Zaslavsky AM et al.: Relation of surgeon and hospital volume to processes and outcomes of colorectal cancer surgery. Ann Surg 2006: 244:1003-1011.

173. Simunovic M, Rempel E, Theriault ME et al.: Influence of hospital characteristics on operative death and survival of patients after major cancer surgery in Ontario. Can J Surg 2006: 49:251-258.

174. Billingsley KG, Morris AM, Dominitz JA et al.: Surgeon and hospital characteristics as predictors of major adverse outcomes following colon cancer surgery: understanding the volume-outcome relationship. Arch Surg 2007: 142:23-31.

175. Morris M, Platell CF: Surgical volume influences survival in patients undergoing resections for stage II colon cancers. ANZ J Surg 2007: 77:902-906.

176. Bilimoria KY, Bentrem DJ, Feinglass JM et al.: Directing surgical quality improvement initiatives: comparison of perioperative mortality and long-term survival for cancer surgery. J Clin Oncol 2008: 26:4626-4633.

177. Kressner M, Bohe M, Cedermark B et al.: The impact of hospital volume on surgical outcome in patients with rectal cancer. Dis Colon Rectum 2009: 52:1542-1549.

178. Faiz O, Brown T, Bottle A et al.: Impact of hospital institutional volume on postoperative mortality after major emergency colorectal surgery in English National Health Service Trusts, 2001 to 2005. Dis Colon Rectum 2010: 53:393-401.

179. Localio AR, Berlin JA, Ten Have TR, Kimmel SE: Adjustments for center in multicenter studies: an overview. Ann Intern Med 2001: 135:112-123.

180. Chowdhury MM, Dagash H, Pierro A: A systematic review of the impact of volume of surgery and specialization on patient outcome. Br J Surg 2007: 94:145-161.

181. Sundhedsstyrelsen. Behandling af tarmkræft - med fokus på den kirurgiske behandling. 2004. www.sst.dk/publ/Publ2004/Behandling_tarmkraef_dk.pdf

182. Cuffy M, Abir F, Audisio RA, Longo WE: Colorectal cancer presenting as surgical emergencies. Surg Oncol 2004: 13:149-157.

183. Jestin P, Nilsson J, Heurgren M et al.: Emergency surgery for colonic cancer in a defined population. Br J Surg 2005: 92:94-100.

184. Faiz O, Warusavitarne J, Bottle A et al.: Nonelective excisional colorectal surgery in English National Health Service Trusts: a study of outcomes from Hospital Episode Statistics Data between 1996 and 2007. J Am Coll Surg 2010: 210:390-401.

185. McGillicuddy EA, Schuster KM, Davis KA, Longo WE: Factors predicting morbidity and mortality in emergency colorectal procedures in elderly patients. Arch Surg 2009: 144:1157-1162.

186. Silber JH, Rosenbaum PR, Trudeau ME et al.: Changes in prognosis after the first postoperative complication. Med Care 2005: 43:122-131.

187. Khot UP, Lang AW, Murali K, Parker MC: Systematic review of the efficacy and safety of colorectal stents. Br J Surg 2002: 89:1096-1102.

188. Sebastian S, Johnston S, Geoghegan T et al.: Pooled analysis of the efficacy and safety of self-expanding metal stenting in malignant colorectal obstruction. Am J Gastroenterol 2004: 99:2051-2057.

189. Watt AM, Faragher IG, Griffin TT et al.: Self-expanding metallic stents for relieving malignant colorectal obstruction: a systematic review. Ann Surg 2007: 246:24-30.

190. Tilney HS, Lovegrove RE, Purkayastha S et al.: Comparison of colonic stenting and open surgery for malignant large bowel obstruction. Surg Endosc 2007: 21:225-233.

191. van Hooft JE, Fockens P, Marinelli AW et al.: Early closure of a multicenter randomized clinical trial of endoscopic stenting versus surgery for stage IV left-sided colorectal cancer. Endoscopy 2008: 40:184-191.

192. Varpe P, Huhtinen H, Rantala A et al.: Adoption of self-expanding metallic stents in the palliative treatment of obstructive colorectal cancer-look out for perforations! Surg Laparosc Endosc Percutan Tech 2008: 18:353-356.

193. van Hooft JE, Fockens P, Marinelli AW et al.: Premature closure of the Dutch Stent-in I study. Lancet 2006: 368:1573-1574.

194. Karoui M, Charachon A, Delbaldo C et al.: Stents for palliation of obstructive metastatic colon cancer: impact on management and chemotherapy administration. Arch Surg 2007: 142:619-623.

195. Fernandez-Esparrach G, Bordas JM, Giraldez MD et al.: Severe complications limit long-term clinical success of self-expanding metal stents in patients with obstructive colorectal cancer. Am J Gastroenterol 2010: 105:1087-1093.

196. Bertelsen CA, Meisner S, West F, Wille-Jorgensen PA: Treatment of colorectal obstruction with self-expanding metal stents. Ugeskr Laeger 2006: 168:907-911.

197. Pommergaard HC, Vilmann P, Jakobsen HL, Achiam MP: A clinical evaluation of endoscopically placed self-expanding metallic stents in patients with acute large bowel obstruction. Scand J Surg 2009: 98:143-147.

198. Carne PW, Frye JN, Robertson GM, Frizelle FA: Stents or open operation for palliation of colorectal cancer: a retrospective, cohort study of perioperative outcome and long-term survival. Dis Colon Rectum 2004: 47:1455-1461.

199. Faragher IG, Chaitowitz IM, Stupart DA: Long-term results of palliative stenting or surgery for incurable obstructing colon cancer. Colorectal Dis 2008: 10:668-672.

200. Vemulapalli R, Lara LF, Sreenarasimhaiah J et al.: A comparison of palliative stenting or emergent surgery for obstructing incurable colon cancer. Dig Dis Sci 2010: 55:1732-1737.

201. Storm HH, Engholm G: Relative survival of Danish cancer patients diagnosed 1981 to 1997 and followed to 2001. A status report. Ugeskr Laeger 2002: 164:2855-2864.

202. Storm HH, Gislum M, Kejs AM, Engholm G: Survival of Danish cancer patients 1995-2006. Ugeskr Laeger 2010: 172:2213-2217.

203. Storm HH, Gislum M, Engholm G: Cancer survival before and after initiating the Danish Cancer Control plan. Ugeskr Laeger 2008: 170:3065-3069.

204. Department of Clinical Epidemiology, Aarhus University Hospital. Kort- og langtidsoverlevelse efter hospitalsbehandlet kræft i Region Midtjylland og Region Nordjylland 1998-2009. 2010. http://kea.au.dk/files/352.pdf

205. Birgisson H, Talback M, Gunnarsson U et al.: Improved survival in cancer of the colon and rectum in Sweden. Eur J Surg Oncol 2005: 31:845-853.

206. Shack LG, Rachet B, Brewster DH, Coleman MP: Socio-economic inequalities in cancer survival in Scotland 1986-2000. Br J Cancer 2007: 97:999-1004.

207. Sjo OH, Lunde OC, Nygaard K et al.: Tumour location is a prognostic factor for survival in colonic cancer patients. Colorectal Dis 2008: 10:33-40.

208. Micheli A, Ciampichini R, Oberaigner W et al.: The advantage of women in cancer survival: an analysis of EUROCARE-4 data. Eur J Cancer 2009: 45:1017-1027.

209. McArdle CS, McMillan DC, Hole DJ: Male gender adversely affects survival following surgery for colorectal cancer. Br J Surg 2003: 90:711-715.

210. Kreftregisteret. Kreftregisteret, Norge. 2011. http://www.kreftregisteret.no/no/Registrene/Kreftstati stikk/

211. Pahlman L, Laurberg S, Soreide O: Structuring rectal cancer treatment in Scandinavia. Surg Oncol Clin N Am 2001: 10:855-862.

212. Wibe A, Carlsen E, Dahl O et al.: Nationwide quality assurance of rectal cancer treatment. Colorectal Dis 2006: 8:224-229.

213. Pahlman L, Bohe M, Cedermark B et al.: The Swedish rectal cancer registry. Br J Surg 2007: 94:1285-1292.

214. Coleman MP, Gatta G, Verdecchia A et al.: EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. Ann Oncol 2003: 14 Suppl 5:V128-V149.

215. Coleman MP, Forman D, Bryant H et al.: Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. Lancet 2011: 377:127-138.

216. Klint A, Engholm G, Storm HH et al.: Trends in survival of patients diagnosed with cancer of the digestive organs in the Nordic countries 1964-2003 followed up to the end of 2006. Acta Oncol 2010: 49:578-607.

217. Morris EJ, Sandin F, Lambert PC et al.: A population-based comparison of the survival of patients with colorectal cancer in England, Norway and Sweden between 1996 and 2004. Gut 2011: 60:1087-1093.

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

219. Pedrazzani C, Cerullo G, De Marco G et al.: Impact of age-related comorbidity on results of colorectal cancer surgery. World J Gastroenterol 2009: 15:5706-5711.

220. Hoekstra HJ: Cancer surgery in the elderly. Eur J Cancer 2001: 37 Suppl 7:S235-S244.

221. Quaglia A, Tavilla A, Shack L et al.: The cancer survival gap between elderly and middle-aged patients in Europe is widening. Eur J Cancer 2009: 45:1006-1016.

222. Sargent DJ, Goldberg RM, Jacobson SD et al.: A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med 2001: 345:1091-1097.

223. Golfinopoulos V, Pentheroudakis G, Pavlidis N: Treatment of colorectal cancer in the elderly: a review of the literature. Cancer Treat Rev 2006: 32:1-8.

224. van Steenbergen LN, Elferink MA, Krijnen P et al.: Improved survival of colon cancer due to improved treatment and detection: a nationwide population-based study in The Netherlands 1989-2006. Ann Oncol 2010: 21:2206-2212.

225. Rieker RJ, Hammer E, Eisele R et al.: The impact of comorbidity on the overall survival and the cause of death in patients after colorectal cancer resection. Langenbecks Arch Surg 2002: 387:72-76.

226. Read WL, Tierney RM, Page NC et al.: Differential prognostic impact of comorbidity. J Clin Oncol 2004: 22:3099-3103.

227. Gross CP, McAvay GJ, Krumholz HM et al.: The effect of age and chronic illness on life expectancy after a diagnosis of colorectal cancer: implications for screening. Ann Intern Med 2006: 145:646-653.

228. Gross CP, Guo Z, McAvay GJ et al.: Multimorbidity and survival in older persons with colorectal cancer. J Am Geriatr Soc 2006: 54:1898-1904.

229. Shack LG, Rachet B, Williams EM et al.: Does the timing of comorbidity affect colorectal cancer survival? A population based study. Postgrad Med J 2010: 86:73-78.

230. Frederiksen BL, Osler M, Harling H et al.: Do patient characteristics, disease, or treatment explain social inequality in survival from colorectal cancer? Soc Sci Med 2009: 69:1107-1115.

231. Cronin DP, Harlan LC, Potosky AL et al.: Patterns of care for adjuvant therapy in a random population-based sample of patients diagnosed with colorectal cancer. Am J Gastroenterol 2006: 101:2308-2318.

232. Schrag D, Panageas KS, Riedel E et al.: Surgeon volume compared to hospital volume as a predictor of outcome following primary colon cancer resection. J Surg Oncol 2003: 83:68-78.

233. Schrag D, Panageas KS, Riedel E et al.: Hospital and surgeon procedure volume as predictors of outcome following rectal cancer resection. Ann Surg 2002: 236:583-592.

234. Engel J, Kerr J, Eckel R et al.: Influence of hospital volume on local recurrence and survival in a population sample of rectal cancer patients. Eur J Surg Oncol 2005: 31:512-520.

235. Renzulli P, Lowy A, Maibach R et al.: The influence of the surgeon's and the hospital's caseload on survival and local recurrence after colorectal cancer surgery. Surgery 2006: 139:296-304.

236. Birkmeyer JD, Sun Y, Wong SL, Stukel TA: Hospital volume and late survival after cancer surgery. Ann Surg 2007: 245:777-783.

237. Brannstrom F, Jestin P, Matthiesen P, Gunnarsson U: Surgeon and hospital-related risk factors in colorectal cancer surgery. Colorectal Dis 2010: October 22: [E-pub ahead of print].

238. Ramos M, Esteva M, Cabeza E et al.: Relationship of diagnostic and therapeutic delay with survival in colorectal cancer: a review. Eur J Cancer 2007: 43:2467-2478.

239. Neal RD: Do diagnostic delays in cancer matter? Br J Cancer 2009: 101 Suppl 2:S9-S12.

240. Andersen RS, Vedsted P, Olesen F et al.: Patient delay in cancer studies: a discussion of methods and measures. BMC Health Serv Res 2009: 9:189.

241. Korsgaard M, Pedersen L, Laurberg S: Delay of diagnosis and treatment of colorectal cancer--a population-based Danish study. Cancer Detect Prev 2008: 32:45-51.

242. Korsgaard M, Pedersen L, Sorensen HT, Laurberg S: Delay of treatment is associated with advanced stage of rectal cancer but not of colon cancer. Cancer Detect Prev 2006: 30:341-346.

243. Ramos M, Esteva M, Cabeza E et al.: Lack of association between diagnostic and therapeutic delay and stage of colorectal cancer. Eur J Cancer 2008: 44:510-521.

244. Terhaar sive Droste JS, Oort FA, van der Hulst RW et al.: Does delay in diagnosing colorectal cancer in symptomatic patients affect tumor stage and survival? A population-based observational study. BMC Cancer 2010: 10:332.:332.

245. Fernandez E, Porta M, Malats N et al.: Symptom-to-diagnosis interval and survival in cancers of the digestive tract. Dig Dis Sci 2002: 47:2434-2440.

246. Olsson L, Bergkvist L, Ekbom A: Symptom duration versus survival in non-emergency colorectal cancer. Scand J Gastroenterol 2004: 39:252-258.

247. Gonzalez-Hermoso F, Perez-Palma J, Marchena-Gomez J et al.: Can early diagnosis of symptomatic colorectal cancer improve the prognosis? World J Surg 2004: 28:716-720.

248. Bharucha S, Hughes S, Kenyon V et al.: Targets and elective colorectal cancer: outcome and symptom delay at surgical resection. Colorectal Dis 2005: 7:169-171.

249. Stapley S, Peters TJ, Sharp D, Hamilton W: The mortality of colorectal cancer in relation to the initial symptom at presentation to primary care and to the duration of symptoms: a cohort study using medical records. Br J Cancer 2006: 95:1321-1325.

250. Wattacheril J, Kramer JR, Richardson P et al.: Lagtimes in diagnosis and treatment colorectal cancer: determinants and association with cancer stage and survival. Aliment Pharmacol Ther 2008: 28:1166-1174.

251. Simunovic M, Rempel E, Theriault ME et al.: Influence of delays to nonemergent colon cancer surgery on operative mortality, disease-specific survival and overall survival. Can J Surg 2009: 52:E79-E86.

252. Rupassara KS, Ponnusamy S, Withanage N, Milewski PJ: A paradox explained? Patients with delayed diagnosis of symptomatic colorectal cancer have good prognosis. Colorectal Dis 2006: 8:423-429.

253. Rothman KJ, Greenland S: Precision and validity in epidemiologic studies. In Rothman KJ, Greenland S (eds.): "Modern epidemiology." Philadelphia: Lippincott Williams & Wilkins, 1998: 115-134.

254. Tørring ML. Time from first presentation of symptoms in primary care until diagnosis of cancer: Association with mortality. PhD-thesis. Faculty of Health Sciences, Aarhus University. 2011.

255. Mitchell E, Macdonald S, Campbell NC et al.: Influences on pre-hospital delay in the diagnosis of colorectal cancer: a systematic review. Br J Cancer 2008: 98:60-70.

256. van Steenbergen LN, Lemmens VE, Rutten HJ et al.: Was there shortening of the interval between diagnosis and treatment of colorectal cancer in southern Netherlands between 2005 and 2008? World J Surg 2010: 34:1071-1079.

257. Biondo S, Marti-Rague J, Kreisler E et al.: A prospective study of outcomes of emergency and elective surgeries for complicated colonic cancer. Am J Surg 2005: 189:377-383.

258. Maruthachalam K, Lash GE, Shenton BK, Horgan AF: Tumour cell dissemination following endoscopic stent insertion. Br J Surg 2007: 94:1151-1154.

259. Saida Y, Sumiyama Y, Nagao J, Uramatsu M: Long-term prognosis of preoperative "bridge to surgery" expandable metallic stent insertion for obstructive colorectal cancer: comparison with emergency operation. Dis Colon Rectum 2003: 46:S44-S49.

260. Dastur JK, Forshaw MJ, Modarai B et al.: Comparison of short-and long-term outcomes following either insertion of self-expanding metallic stents or emergency surgery in malignant large bowel obstruction. Tech Coloproctol 2008: 12:51-55.

261. Kim JS, Hur H, Min BS et al.: Oncologic outcomes of self-expanding metallic stent insertion as a bridge to surgery in the management of left-sided colon cancer obstruction: comparison with nonobstructing elective surgery. World J Surg 2009: 33:1281-1286.

262. Cheung HY, Chung CC, Fung JT et al.: Laparoscopic resection for colorectal cancer in octogenarians: results in a decade. Dis Colon Rectum 2007: 50:1905-1910.

263. Frasson M, Braga M, Vignali A et al.: Benefits of laparoscopic colorectal resection are more pronounced in elderly patients. Dis Colon Rectum 2008: 51:296-300.

264. Audisio RA, van Leeuwen B: When reporting on older patients with cancer, frailty information is needed. Ann Surg Oncol 2011: 18:4-5.

265. van Leeuwen BL, Kristjansson SR, Audisio RA: Should specialized oncogeriatric surgeons operate older unfit cancer patients? Eur J Surg Oncol 2010: 36 Suppl 1:S18-22.

266. Sjovall A, Granath F, Cedermark B et al.: Loco-regional recurrence from colon cancer: a population-based study. Ann Surg Oncol 2007: 14:432-440.

267. FOxTROT Protocol Fluoropyrimidine, Oxaliplatin & Targeted Receptor pre-Operative Therapy for colon cancer. UK National Cancer Research Institute's Colorectal Cancer Clinical Studies Group. 2010. http://www.foxtrot.bham.ac.uk/FOxTROT_Protocol__v5.0_210410.pdf

268. Austoker J, Bankhead C, Forbes LJ et al.: Interventions to promote cancer awareness and early presentation: systematic review. Br J Cancer 2009: 101 Suppl 2:S31-S39.

**APPENDIX 1**

The NOMESCO codes used to identify patients who had under-gone procedures for colorectal cancer in Paper II, VII, VIII include: KJFA68, KJFA83-84, KJFA96-97, KJFB20-97, KJFC00-51, KJFF10-13, KJFF20-31, KJFH00-33, KJFH96, KJFW96-98, KJGA32-52, KJGA73-96, KJGA98, KJGB00-50, KJGB96-97, and KJGW96-98.

For Paper VII, we categorized treatment in three groups: those who underwent
(a) a resection (NOMESCO codes: KJFB20-97, KJFH00-33, KJFH96, KJGB00-50 and KJGB96-97),
(b) a diversion only/local procedure (KJFA68, KJFA83-84, KJFA96-97, KJFC00-51, KJFF10-13, KJFF 20-31, KJFW96-98, KJGA32-52, KJGA73-96, KJGA98, KJGW96-98) and
(c) no surgical treatment.

**APPENDIX 2**
Charlson Comorbidity Index
ICD-8 and ICD-10 codes used for the individual conditions were as reported in Table 5 in (204).

**Table 24**

**Charlson Comorbidity Index**

| Charlson weights | Condition |
|---|---|
| 1 | Myocardial infarction |
| 1 | Congestive heart failure |
| 1 | Peripheral vascular disease |
| 1 | Cerebrovascular disease |
| 1 | Dementia |
| 1 | Chronic pulmonary disease |
| 1 | Connective tissue disease |
| 1 | Ulcer disease |
| 1 | Mild liver disease |
| 1 | Diabetes |
| 2 | Hemiplegia |
| 2 | Moderate/severe renal disease |
| 2 | Diabetes with end organ damage |
| 2 | Any tumour (not colorectal cancer) |
| 2 | Leukemia |
| 2 | Lymphoma |
| 3 | Moderate/severe liver disease |
| 6 | Metastatic solid tumour |
| 6 | AIDS |